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THE ANALYSIS OF INFECTION RATES IN DISEASES IN WHICH SUPERINFECTION OCCURS

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Introduction

Considerable attention is now being paid to the meaning of infection rates, as discovered by survey in some diseases, and particularly in malaria where the mechanism of production of the parasite rate and its relation to the inoculation rate have never been clearly understood. In this disease the infection rate in infants is being studied, and important deductions are being drawn from it concerning the efficacy of control measures, and on the supposed existence of immunity to infection, as in the work of GARNHAM (1949).

Several workers including ROSS, BROWNLEE, KERMACK and MCKENDRICK, and SOPER, have attempted the *a priori* analysis of probable happenings by mathematical means. All have started on a necessary series of assumptions, one of which, either stated or clearly implied in all the workings known to the writer, being that superinfection does not occur, an individual once infected being removed out of play until recovery takes place and subsequent exposure to risk arises. This has apparently been regarded as a simplification of the case, and the possibility that it might gravely invalidate much of the argument in relation to many diseases has not been enquired into. There is an exception to this statement in the work of WALTON (1947), who prepared a theory relating the incidence of malaria in a population to the numbers of infective anophelines to which that population was exposed. He considered that the proportion of infected people should be $1-e^{-mq}$ where m is the number of infective bites per person per year and q the mean proportion of the year for which an infected person shows parasitaemia. The formula represents the proportion of people who would become infected in the time q. If the normal history of malaria was that it lasted without interruption for a standard time q and then came to an abrupt end, his formula would represent the proportion affected once stability had been reached, which would happen immediately at the end of the time interval q, which he estimates at 0·26 year. The assumption that this represents the happenings in malaria cannot be maintained. The common history is that infection is prolonged but is marked by a steadily progressive probability of freedom from signs on any particular examination, so that recovery should not be reckoned as a standard time-interval but as a rate describing the increasing probability of freedom from infection in each succeeding unit of time. The validity of Walton's formula and his constants is thrown into doubt by his own data. If they were correct, the limit would be reached at the end of the time q, or 0·26 year, after which there would be no increase. His own series show a steady increase up to 12 months' exposure, and in the two other examples which he uses the increase is prolonged past this time. His calculated tables therefore represent the proportion of the population who receive infections during 0·26 year ; no allowance is made for the possibility of any of those infected recovering during that time. Alternatively, and more in accord with his wording, his calculation would represent the proportion positive at the end of a year if an infected case were only found positive at 0·26 of the examinations made, and that on a quite random distribution. For this to be tenable as a limit, it would again have to be assumed that at the end of one year all infections came to a complete end.

The present writer has long tried to analyse some happenings in malaria on the basis of the work of ROSS (1916). Briefly, this defines the constants of infection and recovery, h and r, and considers the changes in incidence of disease in a population exposed to them on the assumption that they remained constant, and particularly that the increasing incidence in the population did not alter the amount of infective material to which its members were exposed ; this is representative of the state of affairs in new-born children introduced into a place where malaria is perennially endemic. In his definitions (Section III (IV)) Ross excludes consideration of superinfection. He showed that the limit L, or ultimate value, of the proportion affected would be $\frac{h}{h+r}$, and that the proportion x affected at any time t would be :—

$$x=\mathrm{L}-(\mathrm{L}-x_o)e^{-(h+r)t}$$

If applicable to the case of malaria these two formulae should show the ultimate value of the parasite rate when stability has been attained, and at any time before this.

The attempts at analysis of observed data on the basis of Ross's workings have been uniformly unsatisfactory. With given series of parasite rates by age groups it has been possible to fit good curves corresponding well and based on the above equation, but the constants derived in the process have been out of conformity with observed happenings, the calculated recovery rate being greatly below that which would be accepted as credible by any malariologist. As the mathematical working of Ross is not open to question, the assumptions on which his work was based cannot be applicable to malaria.

The only assumption which seemed open to doubt was that of the individual going out of play during the course of one infection and not being re-exposed to risk until after his recovery. On consideration it was realized that this assumption is either incorrect or very questionable in a number of important diseases, which include most of those due to protozoa or helminths, and perhaps several due to bacteria, including possibly tuberculosis. The subject should, therefore, be explored initially as a general one, for later comparison with observed data in specific conditions.

The General Case

The case studied

The argument will be based on the following assumptions :—

(*a*) The amount of infective material to which the population is exposed remains unchanged.

(*b*) The existence of infection is no barrier to superinfection, so that two or more broods of organisms may flourish side by side, the duration of infection due to one being unaltered by others.

These assumptions are materially true of several infections, at least during the early years of exposure to them. It is desired to study, for given amounts of infective material, the resultant infection rates both when stability has been attained and before that state is reached, with some associated happenings.

Definitions

(*a*) The inoculation rate is the proportion of the population receiving infective inocula in unit of time and will be referred to as h. Thus hdt is the proportion inoculated in time dt.

(*b*) The recovery rate is the proportion of affected people (who have received one infective inoculum only) who revert to the unaffected group in unit of time, and will be called r. It does not matter whether the affected group is considered as the one showing evidence of infection, or infected whether showing evidence or not, though different values of r will apply to the two cases.

(*c*) The mortality, m, is defined as the proportion of infections which result in death.

The proportion recovering when superinfection occurs

The recovery rate has been defined above by reference to a single infection, whereas by definition multiple infections may occur, when recovery from one might be masked by another. The average probability that an individual, once positive, will be positive after the lapse of unit time may be represented by R.

The proportion recovering from a single infection in element of time is rdt. The possibility of this recovery is at least partially balanced by the chance of reinfection which for each element of time is hdt. The actual recoveries will, therefore, be represented by :—

$$rdt - hdt = \mathrm{R}dt$$

whence

$$\mathrm{R} = r - h \qquad \ldots (1)$$

I am indebted to my colleague Dr. J. O. Irwin for the demonstration of this identity which is of paramount importance and dictates the difference between the cases of superinfection and no superinfection. His original and alternative proof took the following form :—

It was shown by Ross that the proportion of infected individuals will be :—

$$x=\frac{h}{h+R}\left\{1-e^{-kt}\right\}$$

where R must be considered as the actual recovery rate. In the case he considered, which excluded superinfection, R was synonymous with r, the recovery rate from a single infection, though it is not in the present case where the two will have different values.

When this system has reached a steady state, $t=\infty$, and $x=\frac{h}{h+R}$, and k is equivalent to $h+R$. Now if the recovery rate from a single infection is r, and h is the infection rate, the total chance of being found infected at time t, when t is great, is :—

$$x=h\int_{-\infty}^{t} e^{-r(t-\tau)}d\tau=\frac{h}{r}$$

but $\quad x=\frac{h}{h+R}$

Therefore $\quad r=h+R$

or $\quad R=r-h$

This identity holds good for all values of h. When it does not exceed r, R is positive and represents the tendency of an infected individual towards recovery, and may properly be termed a recovery rate. As h increases it may, in theory and in practice, first equal and then exceed r, when R becomes zero and then negative.

The actual recoveries in both these cases sink to zero and must be treated as such in mathematical equations representing the proportion affected, which involves a change from one formula to another at this point.

The multiplication of infection

The negative value of R has a very real meaning. It does not represent a recovery rate but a condition of overload. This probably represents the condition defined by CHRISTOPHERS (1924) as hyperendemicity, which occurs in malaria. It differs in kind as well as in degree from more moderate endemicity, infants born into such a condition acquiring in the course of one or two years a heavy overload of infection from which the survivors ultimately escape by the development of immunity.

As the present theory deals solely with the proportion affected and pays no regard to the load of infection to each individual, this multiplication may be ignored at the moment. The reduction of actual recoveries to zero when h equals or exceeds r is the only point needing attention.

The mortality rate when superinfection occurs

The mortality m has been defined like the recovery rate with reference to a single infection. The number of deaths must clearly be related to the number of infections distributed in the population and not merely to the number of recipients, which will be less.

The proportion of the population infected in element of time dt is hdt. By definition this will result in the death of $mhdt$, which will be the actual mortality rate of the population from this disease.

The ultimate infection rate

Ross's form of working may be followed in principle though not in detail. Assume that the population consists of P persons, of whom Z are affected and A unaffected, so that Z+A=P. Let the proportion affected, or $\frac{Z}{P}$, be x.

Since the mortality due to other causes will fall equally on all parts of the population and not alter the proportions which it is desired to study, it may be ignored, and the change in size of the population may be considered as solely due to mortality from the disease. Then :—

$$dP = -mhdtP$$

$$\frac{dP}{dt} = -mhP \qquad \ldots (2)$$

The change in the size of the affected group will be due to new accessions, recoveries and deaths, or

$$dZ = hdtA - (r-h)dtZ - mhdtP$$

$$\frac{dZ}{dt} = hA - (r-h)Z - mhP \qquad \ldots (3)$$

Substituting xP for Z, and P(1−x) for A

$$\frac{d(xP)}{dt} = hP(1-x) - (r-h)xP - mhP$$

$$\text{But } \frac{d(xP)}{dt} = \frac{xdP}{dt} + \frac{Pdx}{dt}$$

Subtracting and cancelling the universal P :—

$$\frac{dx}{dt} = h(1-x) - (r-h)x - mh + xmh$$

$$= h - rx - mh + xmh$$

$$= h(1-m) - x(r-mh) \qquad \ldots (4)$$

The maximum value of x in this, which may be termed the limit or L, may be found by equating the right side with zero, from which :—

$$L = \frac{h(1-m)}{r-mh} \qquad \ldots (5)$$

This expresses the ultimate level when stability has been reached. As mh will in most cases be small in relation to h and r it approximates to the linear function $L = \frac{h}{r}$ which is the expression when the mortality is zero. The value holds good so long as h hoes not exceed r. When this occurs equation (3) becomes invalid, as a negative quantity of recoveries has no material significance. Recoveries are then zero, the equation must be altered to read :—

$$\frac{dZ}{dt} = hA - mhP \qquad \ldots (6)$$

from which it may readily be derived by working similar to the above that L=1.

The incidence before stability is reached

Again the principle of Ross's working may be followed. The case will first be taken where h does not exceed r. In equation (4) substitute the value of L given in (5) to read :—

$$\frac{dx}{dt}=h(1-m)-x(r-mh)$$
$$=L(r-mh)-x(r-mh)$$
$$=(L-x)(r-mh)$$

Put $L-x=y$

$$\text{Then } -\frac{1}{y}\frac{dy}{dt}=r-mh$$

$$\log_e y=-(r-mh)t+\text{a constant}$$

If y_o is the value of y at the beginning of the happening, $\log_e y_o$ is the constant.

$$y=y_o\,e^{-(r-mh)t}$$

Substituting $L-x$ for y :—

$$L-x=(L-x_o)e^{-(r-mh)t}$$
$$x=L-(L-x_o)e^{-(r-mh)t} \qquad \ldots (7)$$

This gives the value of x for any time t from the start of the happening so long as h does not exceed r. When this occurs a modification allowing for zero recoveries similar to that made in calculating the limit must be adopted. By working similar to that used above it can then readily be established that :—

$$x=1-(1-x_o)e^{-(h-mh)t} \qquad \ldots (8)$$

In the present case x_o is zero and may be omitted from (7) and (8).

The transition from one to another is quite smooth as it occurs when h is equal to r. The change is simple in synthetic working, but may cause confusion in analytical working unless data on the early stages of the curve are available. Since the limit L is never reached but only perpetually approached it is interesting to notice the time at which lower levels are reached. The most convenient value for general use is 0·9L, which is reached when :—

$$t=\frac{2\cdot30}{K}$$

when K represents either $r-mh$ or $h-mh$ whichever is appropriate to be used ; the latter when h exceeds r, the former when it does not. The equivalent times for ascent to other parts of the curve are given in Table I.

With these values a curve can be readily built for any given values of h, m and r.

The effect of mortality on the curve and on the limit reached is very slight for all mortalities within the normal range. However large it may be it does not affect the values of h and r producing a limit of 1·0. When h is below the value of r it does to some extent depress the value of L, but not in a way which is likely to lead to serious error if it is mistakenly assessed. By decreasing the power to which e is raised in equations (7) and (8) it slows the rate of ascent of the curve to the limit but only in direct proportion to its own value, so that the modification is in most cases likely to be small.

The normal mortality of some of the diseases in this group may be low and where this is the case it may be justifiable to ignore it and to treat the limit as $\frac{h}{r}$, and also to omit the element mh as a part of the power of e in (7) and (8).

TABLE I

Time at which succeeding stages in the curve are reached

Value of x	Time, t
0·1 L	0·107/K
0·2 L	0·207/K
0·3 L	0·358/K
0·4 L	0·511/K
0·5 L	0·693/K
0·6 L	0·917/K
0·7 L	1·21/K
0·8 L	1·61/K
0·9 L	2·30/K
0·95 L	3·02/K
0·975 L	3·69/K
0·99 L	4·60/K

Discussion

The relationship shown between inoculation frequency, recovery rate, mortality, and the resultant infection rate in a community when the possibility of superinfection is admitted differs not only in degree but in principle from the relationship to be expected when superinfection is excluded. In that case it has been shown by Ross that the limiting value of x, or L, is of the form $\frac{h}{h+r}$. Of these r may be assumed to be nearly constant in any one disease, and h to vary from series to series. As h enters significantly into both the numerator and the denominator of this identity, the limit never reaches unity, to which the graph of h and L is an asymptote. In that case extremely high inoculation rates are necessary to produce high limits, for instance a limit of 0·95 could not be attained until h became 19 times the value of r. When superinfection is admitted the position is quite changed, the inoculation rate h plays quite an insignificant part in the denominator of the expression for L. When the mortality is zero the relation between the two is represented by a straight line between the values $h=0$ and $h=r$. When mortality is significant the relation is not linear, the graph being curved with its concavity towards t, but also achieving the value 1·0 when $h=r$. High values of x are, therefore, attributable to very much lower inoculation rates than in Ross's case. To illustrate : $x=0{\cdot}95$ L when $h=0{\cdot}95\ r$ in this case (assuming zero mortality) and when $h=19\ r$ in Ross's case. As much of the interest of the study of some diseases lies in the extreme cases when infection rates are high, the modification of theory is of first importance.

The theory has been developed for utilitarian purposes. There are some unresolved problems concerning the development of acquired immunity in malaria, which turn on the question whether the degree of immunity attained is solely dependent on the amount of previous exposure to infection, or partially to this cause and partially to racial characteristics favouring its development. It is believed that the study of infant parasite rates, illustrated by this theory and leading to estimation of inoculation rates, may make it possible to throw

more light than has been possible hitherto on the relation between them and subsequent immunity. It should also be of value in the appraisal of the results of control measures against that disease, and in the understanding of the endemicity of many others, including particularly the helminthic infections.

At present the theory refers solely to happenings when the inoculation rate is static. It is a theory of endemicity and not of epidemicity, but development in relation to the latter is clearly possible.

The theory is a general case, developed as a result of an interest in malaria and first to be applied to that disease. It should, however, be applicable to any conditions in which superinfection can occur, an enquiry into the possibility of which is necessary in every case. One of the conditions to which it might have particular reference is tuberculosis. HEIMBECK (1949) has studied the possibility of superinfection and confirms a previous finding that " tuberculous infection of primary TB infected persons can give rise to a tuberculous disease, that is superinfection ". He was concerned in risks to individuals, but if he is correct his finding has an important bearing on community aspects, and especially on the interpretation of Mantoux test surveys which are now being made on a large scale.

Summary

The relationship between the amount of infective material to which a population is exposed and the resulting infection rates is considered. It is pointed out that the relationship when superinfection occurs may be different from the relationship when the possibility of superinfection is excluded.

Most previous workers have excluded the possibility of superinfection. The case when it is allowed is studied mathematically. The relationship found is quite different in principle, as well as in degree, from that when superinfection does not occur.

The probability of an infected person remaining infected at a subsequent examination is studied, and a general formula is deduced. In some cases this represents an actual recovery rate, though less than the standard recovery rate from a single infection. Where the inoculation rate is high the recovery rate sinks to zero.

In some cases the probability of being found positive at subsequent examination is shown to increase. This is considered to represent a progressive multiplication in the load of infection which must result in supersaturation. It is thought that this represents mathematically the condition described as hyperendemicity in malaria.

The limit or ultimate level of infection rates is considered, and general formulae showing their relation to inoculation rates, recovery rates, and fatality are deduced. These differ radically from similar findings when superinfection is excluded, and particularly in that the value of the limit has an almost linear relation to the inoculation rate.

The proportion affected at varying ages is studied and general formulae are deduced. The nature of the curve is discussed.

It is suggested that study of infection rates in infants, on the lines developed, may have important practical implications in malaria. It is also pointed out that the case is a general one, referring to all diseases in which superinfection occurs, and that it might have a bearing on the epidemiology of tuberculosis.

I am very grateful to Dr. J. O. Irwin both for his original contribution to this paper and for very helpful criticism and advice on the whole subject matter.

REFERENCES

CHRISTOPHERS, S. R. (1924) *Indian J. Med. Res.*, v. 12, 273. [*Trop. Dis. Bull.*, 1925, v. 22, 396.]
GARNHAM, P. C. C. (1949) *Ann. Trop. Med. & Parasit.*, v. 43, 47. [*Trop. Dis. Bull.*, 1949, v. 46, 1113.]
HEIMBECK, J. (1949) *Acta Tuberculosea Scandinavica*, Suppl. 21, 36. [*Bulletin of Hygiene*, 1950, v. 25, 243.]
ROSS, R. (1916) *Proc. Roy. Soc.* Ser. A., v. 92, 204.
WALTON, G. A. (1947) *Ann. Trop. Med. & Parasit.*, v. 41, 380. [*Trop. Dis. Bull.*, 1948, v. 45, 401.]

THE ANALYSIS OF MALARIA PARASITE RATES IN INFANTS

by

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Introduction

The writer has developed elsewhere (MACDONALD, 1950, above) a theory relating inoculation rates to resultant infection rates for those diseases in which fresh infection during the course of pre-existing infections is a normal occurrence. The theory shows that when such superinfection is possible the relation between the two is not only very different in degree from the relation which must exist when superinfection in the course of a previous infection is ruled out, but differs also in principle. If it is applicable to malaria it should cause a considerable modification of common conceptions on the significance of parasite and spleen rates, and it might be a useful tool with which to work on some current problems, particularly the relation between the amount of infective material received and the subsequent development of immunity.

The justice of the application of the theory to malaria therefore needs examination. The only unusual assumption on which it is based is that the existence of one infection is no barrier to superinfection, so that two or more broods of parasites may flourish side by side, the duration of one infection being unaltered by others.

As an absolute truth in malaria the assumption is untenable. The phenomenon of homologous immunity is well established. This homologous immunity is strain-specific, not species-specific, at least until many infections have occurred. An individual once infected with a strain of *Plasmodium vivax* cannot be superinfected with that strain when sufficient time has elapsed for the development of the immunity, but remains susceptible to infection with other strains of the same species. In the case of *P. falciparum*, the commonest tropical parasite, a similar homologous immunity exists, but it appears to be much weaker than the immunity developed against strains of *P. vivax*. JAMES, NICOL, and SHUTE (1932) infected a patient on three consecutive occasions with the same strain of *P. falciparum*. The first infection produced a typical clinical attack, the second and third produced milder attacks. Fourth and fifth attempts failed, but the fact that the immunity developed was strain-specific only, was demonstrated by subsequent inoculation with another strain which produced heavy parasitaemia and a severe clinical attack. During all this process the amount of treatment administered was such that the chance of eradication of the infection could virtually be excluded. These workers noted that they had records of other similar cases.

Superinfection in the course of previous infection is clearly a common, or indeed a regular occurrence in the field. The first demonstration of a state of continuous parasitaemia in children, only explicable on the basis of repeated superinfection, was made by CHRISTOPHERS (1924). The present writer (MACDONALD, 1931) considered similar states and concluded that the infections were discrete in the sense that each was separately recognizable, producing a fresh state of parasitaemia, though occurring during an established infection. EARLE (1939) studied a group of 76 Porto Rican children for over three years in an area where malaria was relatively mild. Of the group examined, 52 showed fresh access of parasitaemia with high parasite counts and clinical effects, which on consideration the author concluded could only be superinfections during the course of the previous infection, and which seemed to establish the discrete infection theory put forward by Macdonald.

The writer has also tried to analyse data on the age incidence of malaria observed in nature, on the assumption that superinfection was impossible during the course of a previous infection. The mathematical working of ROSS (1916) was used and though theoretical curves could be produced which corresponded well with the observed, their production demanded in every case the derivation of constants which were clearly inapplicable. Thus the recovery rate derived from these studies was in almost all cases below 0·001 and often below 0·0005 per day, which would mean that the common duration of continuous parasitaemia (not only basic infection) from one infection must be of the order of three to six years, a suggestion which most malariologists would reject out of hand. But it is implicit in many series of observations unless the normal happening of superinfection is admitted.

On the other hand an immunity, partial or complete, to malaria is finally established in hyperendemic areas so that the stage is reached when previous infection makes a great difference to fresh ones. In Christophers's classic observation, in a truly hyperendemic area, some degree of mastery over the parasite appeared in the third year of life and was evidenced by a decrease in the average parasite count, which became very marked in the fourth year.

The time interval probably does not apply to less malarious areas where a longer time to gain mastery is probably necessary, and may be taken as a minimum for all areas.

A rational interpretation of the evidence is that certainly during the first couple of years in hyperendemic areas, and perhaps for much longer in places of lower endemicity, the occurrence of one infection with *P. falciparum* makes no material alteration to the probability of another during its course, and that fresh infections during this time are marked by a fresh onset of parasitaemia unaffected by the previous one. Two or more infections may exist side by side and the history of one is not materially affected by the others. The acquisition of partial resistance is shown by markedly decreasing parasite counts, after the occurrence of which the theory should not be applied, but at least during the first couple of years the statement that there seems to be no barrier to superinfections represents the substantial truth.

The recovery rate in *P. falciparum* malaria

The definition here used for the recovery rate is the proportion of affected people (who have received one infective inoculum only) who revert to the unaffected group in element of time. It does not matter whether the affected group is considered as the group showing evidence of infection, or the group basically infected whether showing evidence or not, so long as it is stated which is meant. For practical application to malaria, the affected group will be considered as that showing parasitaemia at the time of examination, and common knowledge says that termination is usually gradual with increasing intervals of freedom from parasitaemia. The recovery rate must, therefore, represent the increasing probability of being free from parasitaemia when examined.

TABLE I

The proportion of subjects remaining positive at succeeding intervals after a single infection with *Plasmodium falciparum*

Time in days	Actual from data by Earle *et. al.*	Calculated from $x = e^{-0.0048(t-31)}$
0	1·0	1·0
7	0·974	1·0
14	1·00	1·0
21	0·879	1·0
28	0·973	1·0
45	0·870	0·933
80	0·701	0·791
115	0·699	0·668
150	0·574	0·573
185	0·517	0·478
220	0·390	0·404
255	0·354	0·341
290	0·331	0·289
325	0·227	0·244
360	0·171	0·216
395	0·178	0·183

The best series of observations on this subject is probably that collected by EARLE *et al.* (1939), who followed by weekly examinations a group of untreated Porto Ricans for 60 weeks from the date on which they first became infected with *P. falciparum*. The chance of superinfection during this time was considered negligible. Their essential data are presented in Table I and Figure 1.

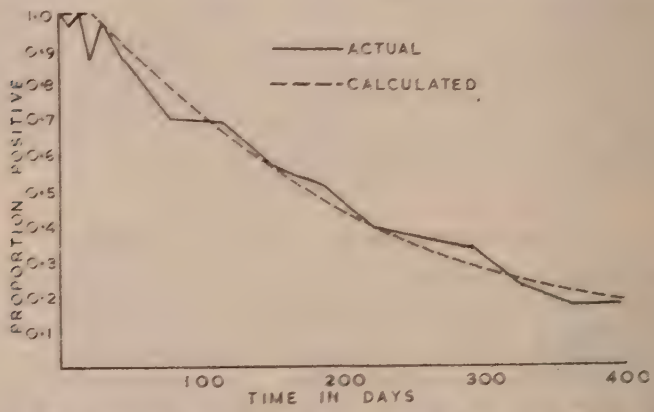


Fig. 1.—The recovery rate in malaria. Actual data from Earle (1939). Theoretical curve as described in the text. Observed and calculated values are given in Table I.

In interpreting them the assumption was first made that the probability of recovery followed the normal laws of decreasing logarithmic progression, the number of fresh recoveries being a constant proportion of the number still affected at the previous examination. In this case the proportion remaining affected would be represented by a formula of the type :—

$$x = e^{-rt}$$

Where x is the proportion affected,
r is the recovery rate per day, and
t is the time since first observation in days.

Efforts were made to fit a curve of this type to Earle's data. None of them was quite successful and it was realized that there was a missing constant which must be introduced. Analysis of the data by the method of least squares showed that the correct formula was :—

$$x = e^{-0{\cdot}0048\,(t-31)}$$

The curve of this formula is superimposed on the observed data in Figure 1. Its close agreement will be noted and there is little doubt that it represents the truth for this series. The time element $(t - 31)$ in plain words represents the fact that there is no progressive tendency to recovery for the first month, after which there is a steady tendency to it, following well-understood laws. The recovery rate is 0·0048 daily and means that the number found positive on each successive day may be expected to be the number found positive on the previous day multiplied by (1–0·0048) or 0·9952.

It is impossible to say from the above data whether this figure would apply to series infected with other strains of parasite, and there are no adequate data from direct evidence known to the writer on which this could be checked. Indirect evidence, given later, shows that it is a good approximation to

happenings in several parts of Africa. WALTON (1947) presented a series from Sierra Leone from which he deduced that an infected person was positive for an average period of 3·15 months. However, only four of his subjects were followed for 12 months or more from first infection, and they were positive on 11 out of 17, 7 out of 9, 1 out of 9 and 5 out of 11 occasions. Four others were followed for nine months or more from first infection and were positive on 4 out of 6, 2 out of 6, 4 out of 9 and 8 out of 9 occasions. These few examined for relatively long periods from first infection do not support the short duration deduced by Walton, and the series is regretfully discarded.

The figure deduced from Earle will be taken as generally applicable, though, to avoid the appearance of extreme accuracy which has not been attained, it will be simplified to 0·005.

The inoculation rate

This is defined as the proportion of the population receiving infective inoculations in unit of time, which for practical purposes will be taken as one day. This subject has been studied at some length by DAVEY & GORDON (1933) in West Africa and their "individual inoculation rate" is the same as the "inoculation rate" now considered. Briefly they calculate :—

(*a*) An anopheline density for the average room.
(*b*) An infective anopheline density, correcting the former by the proportion shown to have sporozoites in the glands.
(*c*) An inoculation rate by correction of the former for the frequency with which an anopheline is believed to bite, put at 0·5 times daily.
(*d*) An individual inoculation rate by correction for the number of people occupying the average room.

They quote various observed rates from Sierra Leone and Nigeria, giving more detailed information for those from Freetown and from a neighbouring village, Kissy, than from others. Some anopheline infective densities (requiring correction as in (*c*) and (*d*) above) given are :—

Freetown	0·024
Ibadan	0·098
Lagos and suburbs	0·403
Kissy	0·844

They point to the great seasonal variations in the rates, indicating that in Kissy the anopheline infective density varied from 0·075 to 0·84. Unfortunately their data are not given in tabular but only in graphic form, but they state that, as an average for the whole year, the inoculation rate in Kissy is 0·21, from which it may be taken that the individual inoculation rate is about 0·1.

Walton has re-examined the same question with materially similar findings except that he allows for a random distribution of anophelines and consequent uneven distribution of bites, for the difference between infected and infective bites, and for the deviation of mosquitoes to animals. The total of the allowances he makes amounts to a multiplication of Gordon and Davey's figure by 0·4. His calculations applied to the Kissy data already quoted would give an average daily individual inoculation rate of 0·04. He collected original data in Freetown and found rates, which he expressed as annual instead of daily ones, in successive seasons, of 0·29, 0·0073 and 0·016. The corresponding daily figures would be 0·0008, 0·00002 and 0·00004.

Other workers have collected local figures on similar lines. It is, however, clear that the direct observation of inoculation rates by means such as these

must be subject to many inaccuracies. Anophelines caught for the purpose of its estimation are using the houses as resting places by day ; there is little if any useful evidence on the relation between their numbers and the numbers biting in the house at night under normal conditions when there may be deterrents such as smoke, or alternative sources of food. The periodicity of feeding is not properly established and the choice of a subject may not be random. Further, the distribution of infective anophelines throughout a village is very unlikely to be entirely random. Proximity to breeding places, direction of wind and relative suitability of resting places are likely to introduce a considerable element of choice into the selection of resting places. Indeed, Gordon and Davey noted one house in which the individual inoculation risk was consistently about five times the average, and it would look as if this single house might have noticeably affected their total figures. Unless examinations are made not only throughout the year but also over a very large number of houses, the chance of serious error from this cause is great if the results are to be applied to any but the actual houses searched. Walton to some extent took this into account and based his figures on collections from 162 houses each week throughout the year, but some figures in other sources are based on smaller collections.

The field estimation of the inoculation rate is, therefore, at best an inaccurate method and can only throw general light on actual happenings.

The mortality rate in malaria

The mortality rate in untreated *falciparum* malaria among people of races which have been exposed to the disease for centuries is a matter of controversy. Most observers in hyperendemic areas would consider that the mortality which occurs in those areas is largely in the infant and child groups. Bagster Wilson (1936) clearly considers that it may be material. Garnham (1949) is of the opinion that at least in some tribes it is negligible, but bases this conclusion on evidence which includes the *post-mortem* establishment of malaria as a cause of death in a number of children. The evidence for the various opinions is on the whole statistically unsound. It is sufficient here to note that although mortality affects the happenings, the working of numerical examples shows that the highest mortality which might be expected to be due to malaria does not do so in a manner which makes any material difference. To avoid the semblance of bias in favour of the writer's own opinions, it will be ignored in subsequent numerical working.

Expected happenings in malaria

The theory already elaborated states that if :

h is the inoculation rate,
r is the recovery rate from a single infection,
R is the recovery rate ruling under the local conditions of superinfection,
m is the case mortality from a single infection,
x is the proportion affected (that is showing parasitaemia),
t is the time of exposure,
L is the maximum level reached by the parasite rate when stability is attained, and
e is the mathematical constant 2·71828,

then :—

1. *The local recovery rate*

$$R = r - h$$

That is the actual recoveries which could happen, if potential ones masked by

superinfection are excluded, will be equivalent to the recovery rate from a single infection less the inoculation rate.

2. *The ultimate value of the parasite rate*

$$L=\frac{h-mh}{r-mh}$$

when the inoculation rate does not exceed the recovery rate. When this occurs, as will be realized from the previous identity, recoveries sink to zero and then L=1·0.

This concerns the maximum level attained by the parasite rate. In considering it, the warning already given that in hyperendemic areas the theorem may only hold for the first couple of years should be kept in mind. After this period it is quite possible that the effects of immunity might reduce the level of the parasite rate. In less malarious areas, where the acquisition of immunity must be longer delayed, it is probably justifiable to use this identity for the interpretation of the parasite rate in older children, perhaps commonly up to five or six years.

The effect of mortality on this identity is slight and for practical purposes may be ignored, or considered as zero, in which case it is simplified into :

$$L=\frac{h}{r}$$

or L=1·0 when h exceeds r.

Now r is constant. The relation between the limit and the inoculation rate is, therefore, a simple direct one. An increase in the inoculation rate by say 10 per cent. would, after a suitable interval of time, produce a corresponding increase of 10 per cent. in the parasite rate ; this would hold good for all values of h and L up to the point where the latter reaches 1·0.

This is in direct contrast with common thought and teaching. It has consistently been said that as the inoculation rate increases it produces steadily smaller increases in the parasite rate, until when the latter passes 90 per cent. the effects of quite big changes in the inoculation rate are not discernible. This is a theory to which malariologists have become accustomed. It represents the happenings which would occur if the possibility of superinfection were excluded, when the working of Ross would apply, but it is entirely untenable if fresh infections commonly occur during the continued existence of previous ones.

Common sense will dictate to many the objection that random distribution of infections must result in a decreasing increment of positives when unity (or 100 per cent.) is approached. This is the case ; it does not, however, affect the limit but the time at which it is reached. Reference to later paragraphs will show that the incidence by ages does not increase as a straight line but as a curved one attributable to this phenomenon.

At one time there was much discussion on the rarity of spleen and parasite rates of 100 per cent. or near that figure. This has now become less common and many examples of such rates have been produced. It is probable that earlier observations were largely made on older children in whom immunity may have played a part in reducing the rates, whereas there is a growing tendency to examine infants who previously were often ignored. The limit is very slowly approached except where the inoculation rate is very high. Further information will be given on this later ; here it is sufficient to notice that a limit of 0·99 would not be attained within two years unless the inoculation rate exceeded 0·0063. The dates when the limit is attained and when immunity starts to play a significant part in the picture are therefore near to each other in

hyperendemic areas, where conclusions should only be based on the study of infants. In less malarious places where the inoculation rate is 0·005 or below, and where immunity is likely to play a smaller part or even an insignificant one, the limit may be of the greatest value as a direct measure of the inoculation rate. In them the value 0·9 L and 0·99 L are attained at the ages of 470 and 930 days. In these less malarious areas the level is unlikely to decline rapidly and a parasite rate taken at any age between 2 and 6 years should give direct information on the inoculation rate by the identity :

$$h = r\mathrm{L}$$

or the inoculation rate equals the parasite rate expressed as a proportion (*not* a percentage) multiplied by 0·005.

3. *The change in the rate with age*

$$x = \mathrm{L}(1 - e^{-(r-mh)t})$$

As with the limit, this must be modified when the inoculation rate exceeds the recovery rate to read :

$$x = 1 - e^{-(h-mh)t}$$

The effect of mortality is again slight and it may be justifiable in many cases to consider it as zero, when the formulae are simplified to :

$$x = \mathrm{L}(1 - e^{-rt})$$

and

$$x = 1 - e^{-ht}$$

These formulae give the proportion which may be found affected at any age, here represented in days. It ultimately achieves the level of L already discussed, to which it is asymptote. When dealing with older children in areas of moderate endemicity the much simpler formula defining L may be used, the chief use of the present one being in the consideration of rates in infants before the peak and stability are reached, particularly in the analysis of observations giving parasite rates by successive ages. In dealing with the youngest children care must be taken to allow for the incubation period of say

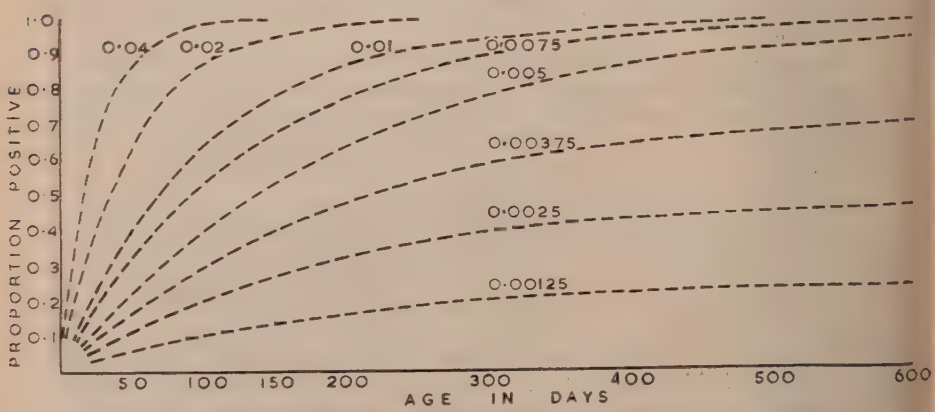


Fig. 2.—Theoretical infection rates by ages corresponding to various inoculation rates (h). The limiting value for all values of h exceeding 0·005 is 1·0. Corresponding tabular data are in Table II.

10 days, which should be subtracted from the actual age so that t truly represents the period of exposure to risk of *parasitaemia* which is the subject studied, and which does not start until 10 days after birth if congenital malaria is considered unlikely to happen. When infants are recorded as belonging to successive age groups they should all be given the median age in their group. Thus children recorded as being of the age 0 to 2 months have a median age of 30 days, and after allowance for the incubation period, of 20 days.

The formula represents a curve of which illustrative examples for different values of the inoculation rate are given in Figure 2 and Table II. The higher

TABLE II

Values of x and L for different values of h and t

	Value of x when $h=$							
t	0·00125	0·0025	0·00375	0·005	0·0075	0·01	0·02	0·04
25	0·29	0·59	0·088	0·119	0·181	0·222	0·394	0·632
50	0·055	0·111	0·166	0·222	0·312	0·394	0·632	0·865
100	0·099	0·197	0·296	0·394	0·528	0·632	0·865	0·982
150	0·132	0·264	0·395	0·528	0·675	0·777	0·936	0·975
200	0·158	0·316	0·474	0·632	0·777	0·865	0·982	
250	0·178	0·357	0·535	0·714	0·846	0·918	0·993	
300	0·194	0·388	0·592	0·777	0·895	0·936		
350	0·206	0·413	0·619	0·826	0·928	0·970		
400	0·216	0·432	0·648	0·865	0·950	0·982		
450	0·223	0·447	0·670	0·895	0·966	0·989		
500	0·229	0·459	0·688	0·918	0·976	0·993		
600	0·234	0·468	0·702	0·936	0·988			
700	0·242	0·485	0·727	0·970	0·995			
800	0·245	0·491	0·736	0·982				
900	0·247	0·494	0·743	0·989				
1000	0·248	0·497	0·745	0·993				
L	0·25	0·50	0·75	1·0	1·0	1·0	1·0	1·0

curves illustrated are incomplete, being terminated according to the writer's ideas on the time when the access of immunity might start to invalidate them, when the average infant has suffered five separate infections. The figure is empirical and it is to be hoped that later work will give a firmer foundation than is now available on which to base one.

All of these curves are based on the assumption that mortality is zero. As already pointed out, the actual mortality would not greatly change them, but any change would be mainly in the form of slowing of the rate of ascent of the curve.

Study of Figure 2, and of Table II which sets out the data on which it is based, will show that the curves have certain characteristics. All are asymptotes to the appropriate value of L for their case, and though they perpetually approach this value they never absolutely attain it. They are concave with their concavity towards the time axis, the slope being steepest at the beginning and thereafter steadily declining. When the inoculation rate does not exceed the recovery rate, the rate of ascent to the limit is always the same, that is the values 0·25 L, 0·5 L, 0·9 L, etc., are attained at the same time. When the inoculation rate exceeds the recovery rate this is not the case and the rate of ascent to the limit, which is then always unity, varies with the inoculation rate.

The analysis of observed data

The approach to the calculation of k and L by mathematical means which take full account of the numbers of people in each group and therefore of the probable error of each group, and which allow a proper weightage for each group according to the period of exposure, would involve a considerable mathematical analysis on simple groups of figures. The writer has preferred to estimate k or L from each pair of observations of x and t to find the mean value obtained, and to build up theoretical curves based on this. Small errors could be avoided from random sampling in the younger age groups, where the proportion infected is small and the chance of error greatest, produce an exaggerated effect to the calculation of the mean k and L, and where they appear to be present and due to this cause the age group concerned may be omitted in the calculation. The omission may usually be considered as a more realistic representation of happenings than the inclusion of an apparent random error which would multiply itself greatly in the final result.

The analysis of age distribution data is in reality a simple mathematical process. The final element data to be estimated from each pair of observations of x and t from the identity :

$$L=\frac{x}{1-e^{-(1+\mu)t}}$$

To help in using this, Table III gives the value of the denominator for some

TABLE III

VALUES OF $1-e^{-0.005t}$ AND $-t$ VALUE FOR DIFFERENT VALUES OF t

days	Corresponding Age Group mid-point for incubation period	$1-e^{-(1+\mu)t}$	$-0.454t$
	Months		
5	Under 1	0·02456	−2·2715
35	1—	0·16171	−15·8855
64	2—	0·28119	−29·0464
97	3—	0·40[illegible]	−43·[illegible]127
127	4—	0·49[illegible]	−57·[illegible]56
158	5—	0·54915	−69·[illegible]66
188	6—	0·[illegible]29	−81·[illegible]40
218	7—	0·66998	−94·[illegible]57
248	8—	0·71213	−108·[illegible]14
278	9—	0·7[illegible]95	−120·[illegible]
[illegible]	10—	0·[illegible]777	−134·[illegible]
349	11—	0·81732	−147·[illegible]
	Years		
549	1—	0·[illegible]290	−254·[illegible]
911	2—[illegible]	0·[illegible]886	−391·[illegible]

Note. Where age groups such as 1–4·9 months are involved, the corrected median age is that for the median month, in this case 4 months, or when converted 127 days.

corresponding age groups. If the mean value of L is found to be below 1·0 the mathematical rate can easily be read off from the identity :

$$k=0{\cdot}454.$$

If the mean value of L so found is over 1·0 then h exceeds r and the true value of L is 1·0. The inoculation rate should then be calculated from the identity :

$$h=\frac{\text{Log}\,(1-x)}{-0{\cdot}4343t}$$

Values of log $(1-x)$ and of $-0{\cdot}4343t$ to simplify this calculation are given in Tables IV and III.

TABLE IV

Values of log $(1-x)$ for various values of x

x	$log(1-x)$	x	$log(1-x)$
0·05	—0·02228	0·55	—0·34679
0·10	—0·04576	0·60	—0·39794
0·15	—0·07058	0·65	—0·45593
0·20	—0·09691	0·70	—0·52288
0·25	—0·12494	0·75	—0·60206
0·30	—0·15490	0·80	—0·69897
0·35	—0·18709	0·85	—0·82391
0·40	—0·22185	0·90	—1·00000
0·45	—0·25964	0·95	—1·30103
0·50	—0·30103		

When it is not specially desired to study the age incidence, and the observed limit is obviously well below 1·0, the value of the inoculation rate can be simply estimated by observation of the highest values of the parasite rate at any age. This is the limit L, and the inoculation rate is represented by :

$$h=0{\cdot}005\text{L}$$

Comparison with observed data

There are a number of observations of the parasite rate in infants by age groups, on the mechanism of causation of which there has been considerable speculation and which the writer believes are all explicable on the basis of the theory already elaborated. They are presented in a series of graphs on each of which the theoretical curve which is believed to correspond best is superimposed. It will be noted that the fit of the curves is in all cases good. The legend of each figure gives the source of the observed data, the values of h and L derived in analysis, and notes on any relevant matter from the original source. In all cases the mortality has been assumed as zero, and the ages given by the original author have been adjusted to the median of the group and for the incubation period as previously described.

The comparisons are only made with series from places where transmission is more or less perennial, for it is obvious that in places where it is markedly seasonal the combined effects of the inoculation rate and the period for which it was operative must be unravelled, and the age incidence must be irregular. If the theory is considered established on these places of perennial transmission, then it is applicable to the others if appropriate adjustments are made.

Figure 3 shows the age incidence in 800 infants seen in infant welfare clinics in Freetown, Sierra Leone, in 1925 and 1926. A large part of the examinations was carried out by the present writer, and the series was quoted by BLACKLOCK and GORDON (1925). These authors speculated on the reasons for the delay

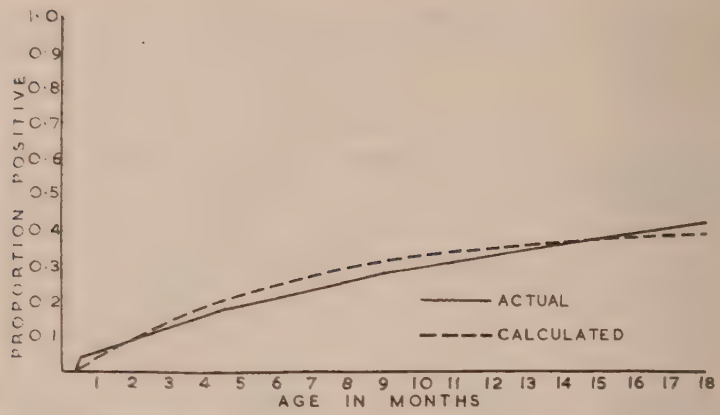


Fig. 3.—Freetown. Data from Blacklock and Gordon (1925). Theoretical curve built on the constants L=0·41, and h=0·0025. Observed and calculated values are :—

Age	*Median Age, corrected, Days*	*Proportion positive*	
		Actual	*Calculated*
Under 1 month	5	0·049	0·010
1 month	35	0·073	0·066
3–4–5 months	127	0·173	0·198
6–11 months	265	0·276	0·301
1 year	540	0·418	0·382
2 years	900	0·418	0·410

in infection in some of the children, expecting them to have become infected much more rapidly than was the case. The theoretical curve built up on it has a limit of 0·41 (*i.e.*, 41 per cent.), and depends on an inoculation rate of 0·00205 daily. In other words each individual would expect to receive an infective bite once in every 487 days. The infants were admittedly seen at infant welfare clinics, in which treatment was given when necessary, but they nevertheless probably reflect general happenings because the parasite rate among the older child population in the same area was very similar to the limit noted here, reaching 46 per cent. at the age of five to six years, which observation alone would have been sufficient to lead to a very similar estimate of the inoculation rate. It is clear from the figure that the theoretical curve fits the observed data extremely well.

Davey and Gordon repeated similar observations in Freetown, and produced the series shown in Figure 4. It will be seen by reference to Gordon and Davey (1932), however, that their group is not quite the same in place of origin as the previous one, and it is in fact much more malarious. A limit of 0·882 is deduced, corresponding to an inoculation rate of 0·0044, on which constant the theoretical curve in the figure is built up. The close coincidence will again be seen. Data up to two years of age only were used in the analysis. Data are given in the original paper on the inoculation rate, but it is not easy to trace in it a figure which represents an average for the entire year. The authors state that it is about 0·0063 during the rains, and it can be deduced that it was about 0·0003 in the dry season, with an annual average of the order of 0·0033, which corresponds reasonably with the figure now estimated.

Walton (1947) repeated similar observations in Freetown fifteen years later, after very effective control measures had been carried out, and the incidence of malaria greatly reduced. His Table V shows that conditions

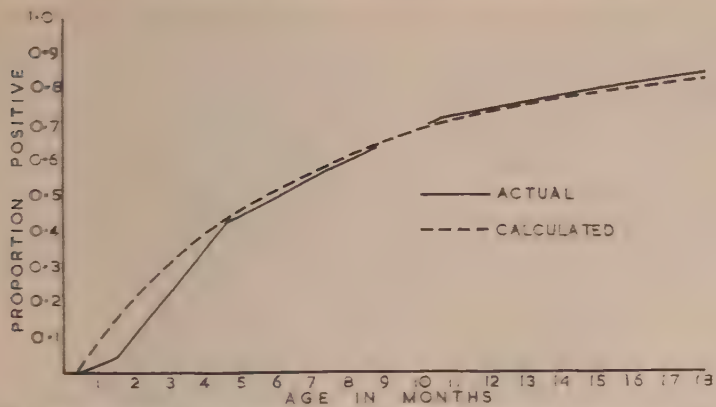


Fig. 4.—Freetown. Data from Davey and Gordon (1933). Theoretical curve built on the constants L=0·882, k=0·0044. Observed and calculated values are :—

Age	*Median Age, corrected. Days*	*Proportion positive*	
		Actual	*Calculated*
0–1–2 months	35	0·048	0·142
3–4–5	127	0·412	0·425
6–7–8	218	0·588	0·585
9–10–11	316	0·706	0·695
1 year	540	0·887	0·823

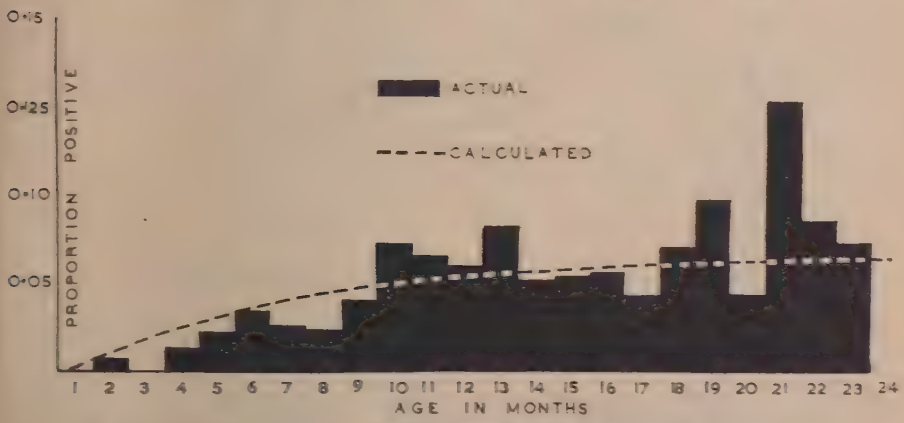


Fig. 5.—Freetown. Data from Walton (1947). The histogram is redrawn from one of Walton's Figures showing the percentage of infants infected at each age. The superimposed curve has the constants L=0·065 and k=0·000335. Further detailed information on the actuals is not available. The values for the calculated curve are :—

Age (Months)	*Proportion positive*	*Age* (Months)	*Proportion positive*
1	0·002	8	0·043
2	0·011	9	0·047
3	0·018	10	0·049
4	0·025	11	0·051
5	0·031	18	0·061
6	0·035	24	0·064
7	0·040		

progressively improved during the period of his observations, whence one would expect older children to have been exposed to more infection than younger ones. His exact data on infant examinations are not clear, being presented in four separate forms, none of which is quite complete. As the most informative, his Figure 4 has been taken for comparison, and a curve corresponding to a limit of 0·065 added to it for comparison. This corresponds to an inoculation rate of 0·00035. By direct observation he estimated the inoculation rate as 0·0073 annually, which corresponds to a daily rate of 0·00002. He comments that so low an inoculation rate could not produce a material incidence of malaria, which must be acquired elsewhere. In another part of his paper he states that 50 of his subjects who were followed for 18 months received 12 to 15 infections in that time, which corresponds to a daily inoculation rate of 0·00043 which is in reasonable accord with the present conclusion, especially when the small number of infected persons concerned is borne in mind. The fit of the curves is reasonable, though it tends to be above observed values in the youngest groups, as would be expected if the incidence were decreasing.

Davey and Gordon examined a series of infants in Kissy, a village in the neighbourhood of Freetown, Sierra Leone, and more malarious than that town. Their data and the deduced theoretical curve are set out in Figure 6. The limit is clearly 1·0, and h is deduced as 0·0133. Again the very close agreement of the curves will be noted. There is, however, disagreement with the

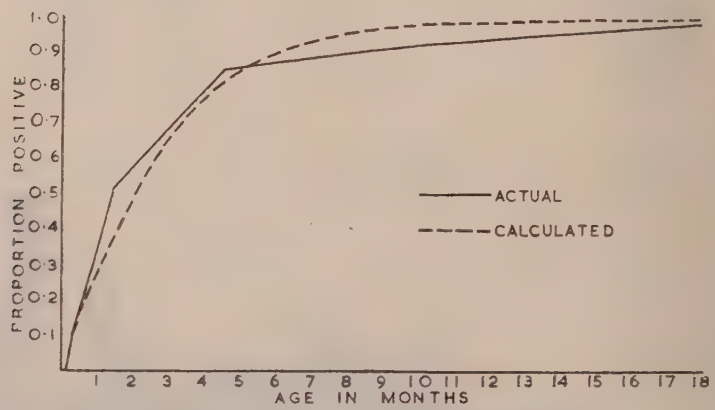


Fig. 6.—Kissy. Data from Davey and Gordon (1933). Theoretical curve built on the constants L=1·0, h=0·013. Observed and calculated values are :—

Age	*Median Age, corrected, Days*	*Proportion positive* *Actual*	*Calculated*
0–1–2 months	35	0·516	0·373
3–4–5 ,, ...	127	0·840	0·815
6–7–8 ,, ...	218	0·895	0·945
9–10–11 ,, ...	310	0·922	0·984
1 year	540	1·0	0·992

inoculation rate as measured by Davey and Gordon on direct anopheline observations, from which they estimated that it was about 0·1, seven times the present figure. There is no obvious explanation of this discrepancy. If the children had been exposed to an inoculation rate as high as that posed by those authors, the age incidence of infections would have been very different from that actually observed. The actual numbers in each group examined are not

stated, but the regularity of the figures would make it probable that they were considerable. The discrepancy is discussed more fully in a later section, but the only conclusion which the figures will stand is that the number of infective bites to which the children were exposed was less than their estimate, though whether this was by reason of non-viable sporozoites, protection by smoke, or that the anopheline density was not universally as great as in the places examined by them, cannot be told.

GARNHAM collected a series of observations in Kenya, which is set out in Figure 7, with a corresponding theoretical curve. The limit is 1·0, the probable inoculation rate is 0·006525. Agreement of the curves is again very close. Garnham states that the inoculation rate was 0·02 in the area studied. He

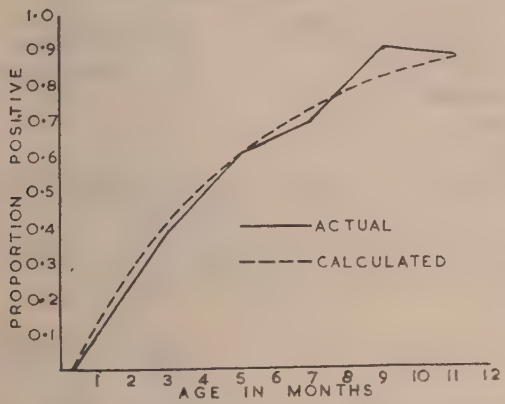


Fig. 7.—Kenya. Data from Garnham (1949). Theoretical curve built on the constants L=1·0, h=0·00625. Observed and calculated values are :—

Age	*Median Age, corrected, Days*	*Proportion positive* *Actual*	*Calculated*
0–1 month	20	0·095	0·122
2–3 months	82	0·39	0·414
4–5 ,, ...	142	0·60	0·604
6–7 ,, ...	203	0·70	0·734
8–9 ,, ...	264	0·90	0·821
10–11 ,, ...	325	0·89	0.880

also calculates theoretical parasite rates by ages which he considers would correspond with an inoculation rate of 0·02, which, however, appears to take no account of the overlap of infections, incubation period, median age within the group or recoveries. In the present writer's opinion the figures estimated are too high, even if the inoculation rate given were correct.

In some ways the most interesting series available is that prepared by BARBER and OLINGER (1931) from children attending at the Health Office in Lagos for vaccination, and in similar groups. The series is illustrated in Figure 8. The entire series included 6,838 children of all ages up to 15 years, but present consideration is limited to the 1,932 aged three years or less. There is a slight doubt about their age grouping and it has now been assumed that the group described as " three months " was, in fact, two and three months of age. The youngest group, aged one month, included only 16 children and as the finding on it is rather anomalous it has been discarded, as Davey and Gordon disregarded it in their analysis. If the series is taken as a whole the most

appropriate limit derived from it is 0·87, corresponding to an inoculation rate of 0·00435, and a curve built on these constants fits quite satisfactorily. On examination it seems that the groups aged two, three and four months are rather below this curve and subsequent groups rather over it. Two curves are,

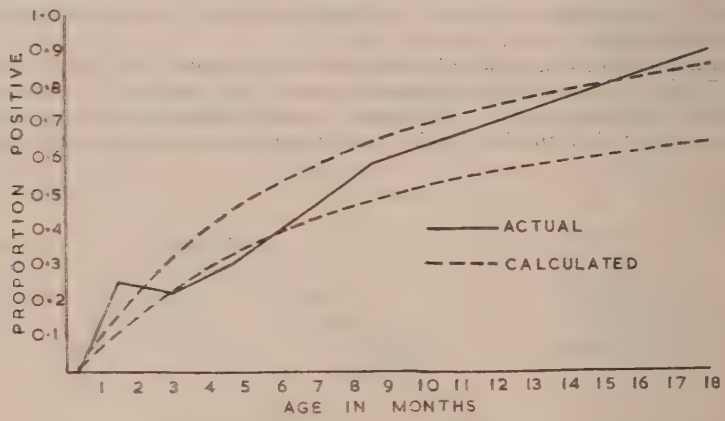


Fig. 8.—Lagos. Data from Barber and Olinger (1931). Two theoretical curves built on constants (*a*) L=0·93 and h=0·00465, and (*b*) L=0·69 and h=0·00345. Observed and calculated values are :—

Age	*Median Age, corrected, Days*	*Proportion positive* *Actual*	*Calculated* L 0·93	*Calculated* L 0·69
1 month	35	0·25	0·150	0·112
2 and 3 months	83	0·224	0·316	0·234
4 months	127	0·297	0·448	0·333
5–11 months	234	0·576	0·641	0·476
1 year	540	0·900	0·868	0·644
2 years	900	0·936	0·929	0·689

therefore, superimposed on the data in the Figure, one corresponding to a limit of 0·93 and an inoculation rate of 0·00465, and the other corresponding to a limit of 0·69 and an inoculation rate of 0·00345. It is suggested that the older infants have on the whole been subjected to a rather higher incidence of malaria than the younger groups, and in fact the authors point out that the endemicity was materially greater in the first two months of their work than in the final two months, exactly a year later, in which corresponding periods 23·6 and 10·7 per cent. of infants were positive. The suggestion that some of the younger infants had been exposed to less endemicity than the older ones therefore seems a rational one, and is the reason for the superimposition of the two curves which appear to represent happenings in the younger and older groups.

These authors also studied the anopheline infective density in considerable detail. Unfortunately it is not possible to identify exactly which collections were made in the areas from which most of the children came. It seems, however, that their table VII refers, and according to it the anopheline density per room averaged 4·8, and the sporozoite rate 6·6 per cent. This would give an infective anopheline density of 0·3160, and presumably an individual inoculation rate of roughly 0·079. The disagreement is as marked as in the case of Kissy, already noted, and is discussed under a later heading.

PUTNAM (1931) in an appendix to this paper gives useful information on resistance as shown by decreased parasite counts. There appear to be two types, one passively transmitted from the mother, of a transitory nature, and causing a lowering of counts which is marked in the first three months and becomes less obvious until it ends at about one year. The other is actively acquired and in their series becomes obvious at the age of three years, when according to the present estimation each child would have suffered about five separate infections. The possible effect of these on the parasite rate is discussed in a later section.

BAGSTER WILSON (1936) examined 25 infants from birth in a hyperendemic area of East Africa. Without giving details he states that the critical age is in all cases conditioned by the date of birth in relation to season, but the appearance of the first infection was never later than five months after birth, while the average was two months. These are the figures one would expect were the inoculation rate of the order of 0·035, roughly one infective bite in every 28 days.

RUSSELL (1938) gives some data from the Gold Coast which differ from all others in that the parasite rate no longer increases but slightly declines after six months of age. There are two possible explanations. The first, which does not demand mathematical analysis, is that there is some very marked seasonal variation in transmission so that children of 12 months have, in fact, experienced no more malaria than those of six months. The rates were :—

Age	Examined	Positive	Proportion Positive
0– 2 months ...	222	86	0·36
3– 5 ,, ...	164	120	0·73
6– 8 ,, ...	133	91	0·68
9–11 ,, ...	61	37	0·60

The first of these two correspond to an inoculation rate of about 0·00825. It is possible that an incidence of this nature occurs for six months of the year, and that the examinations gave a picture seen at the end of the wet season. The other possible explanation of a distribution of this type is a very high recovery rate such as might have been achieved by systematic rather than random administration of quinine. There is no information on which to assess the relative probability of these two explanations.

Discussion of comparison with observed results

The object of the comparison was to enquire whether theory matched life, and could, therefore, be considered to explain natural happenings in the series compared and elsewhere. In considering it there are several points to enquire into : Does the general form of the curves produced compare satisfactorily with those observed ? As a derivative of this, is the type of curve satisfactory so that the general style of the explanation is correct ? Are the constants which are used in theory representative of those in life ? Is there any disturbing factor such as immunity which upsets the conclusions ?

Examination of the figures will show that the curves correspond very closely. From this it may be answered that it is highly probable that natural happenings follow the course independently deduced from mathematical calculations.

The constants used are the recovery rate, the inoculation rate, and time. Of these only the recovery rate is assumed, the inoculation rate is derived in each case and time is known. Reference to Figure 1 will show that there are good grounds for the use of the value 0·005 for the recovery rate in the case of Porto Rico. Can it be assumed to apply elsewhere ? The answer is in the Figures. The rate of ascent of the curve is entirely dependent on the recovery rate in those cases where the limit does not attain 1·0. The dependence is of the form that the lower the recovery rate the slower is the rate of ascent to the limit, though the latter is higher. The correspondence of both limit and rate of ascent in the curves could not have been attained had any material error been made in the assessment of the recovery rate, and in fact a figure for the recovery rate could have been derived direct from the observed data instead of from Earle's series.

To illustrate this, Davey and Gordon's Freetown series of 1931 has been re-worked on the basis that the actual recovery rate was 0·01, twice as great as the figure used in all the preceding calculations. The results are shown in Table V.

TABLE V

Infant parasite rates by ages in Freetown, and theoretical rates calculated on different recovery rates

Age in days (corrected)	Parasite rate (proportion)		
	Actual	Calculated ($r=0{\cdot}005$)	Calculated ($r=0{\cdot}01$)
35	0·048	0·142	0·26
127	0·412	0·425	0·72
218	0·588	0·585	0·782
310	0·706	0·695	0·838
540	0·837	0·823	0·878
L		0·882	0·882

The gross disagreement between the theoretical and the observed when a recovery rate of 0·01 is assumed is obvious. Curves cannot be built to fit any of the observed data except Russell's on a recovery rate widely different from 0·005, which may, therefore, be considered as reasonably established.

Comment may be made that it is odd that increased chances of recovery would increase the parasite rate at some ages. However, the given limit would then be produced only by a higher inoculation rate, so that the last column of Table V corresponds to a doubled recovery rate, and a doubled inoculation rate. Were the latter kept fixed, the ultimate value would be only 0·441.

There remains the question of the possible effect of some extraneous factor, such as a transmitted passive immunity lasting for some months. An established fact about that resistance to high parasitaemia is its transitory nature ; it passes off progressively during the first year. It is known to decrease parasite counts, and assumed to decrease clinical effects correspondingly. It might affect infant parasite rates either by protecting the individual so that he did not become infected when bitten, or it might protect him by increasing naturally his chances of recovery from parasitaemia.

Were either of these to occur, they would inevitably alter the shape of the curve, which would then start on a gentle gradient, become steeper as the

resistance passed off, and again lessen as the limit was approached. It would be at first convex to the time axis and then concave to it. There is no trace of such a happening in the curves produced, except that the Lagos curve might conceivably be interpreted in this way. It might be quite reasonably argued from that curve alone that transmitted resistance protected the youngest infants from about 27 per cent. of infections. However, as there is no comparable happening in other curves, and as Barber and Olinger themselves comment on the changing incidence of the disease which is an equally satisfactory explanation for the shape of their curve, their explanation must be taken as the most likely one.

Acquired resistance at a later age might be expected to restrain the upward trend of the rate and finally to bring it down. It is common observation that this occurs in later childhood. Examination of the data suggests that the first trace of it appears when ht is about 5·0. This has been taken into account and curves have not been prepared beyond this point.

The derived inoculation rates in Kissy and Lagos are lower than those estimated by anopheline counts and dissections.

The writer has seriously tried to equate those high rates with the parasite rates observed, and has used for the purpose not only the present theory, but every other line of reasoning which seemed possible. The Kissy series could be explained on a higher inoculation rate and a greatly increased recovery rate such as might result from regular treatment. The Lagos series cannot be equated except on the theory of a hereditary immunity, *which is not transitory*, and which takes the form of giving absolute protection against some infective bites and none against others, so that, say, only every tenth bite produced any effect. There is no evidence of the occurrence of such an immunity, and there is much incidental evidence that infants are normally susceptible, and it seems very much more rational to stipulate that the number of *infective* bites given was, in fact, materially lower than estimated, especially as the Kissy infants are genetically similar to those of Freetown where observed and estimated figures agree. Even if the explanation were correct, the changes in the infant parasite rate would show with reasonable precision the number of *infections* which the individual had suffered, and it is the infections which produce the clinical results and which act as the stimulus to an acquired immunity.

It is, therefore, suggested that the theory now outlined, when compared with the facts, provides a rational explanation of normal happenings in the epidemiology of malaria.

Relation to other theories

WALTON, in two papers (1947 and 1949), has set out a theory of the relationship between inoculation rates and infection rates, which states that if m be the mean number of infective bites per person per year, and q be the proportion of a year for which an infective person remains positive, then the proportion positive will be $1-e^{-mq}$.

This formula is identical with the one already produced, which states that when recovery does not occur the proportion positive at any time is $1-e^{-ht}$. It records the proportion of the population who have received infective bites during the fraction of a year represented by q and might under certain assumptions represent the final parasite rate encountered. Unfortunately, Walton's definitions are not precise. His q can be taken to mean either that :

(*a*) the normal history of malaria is a continuous duration for this period followed by an abrupt termination without relapse, or

(2) the parasite remains infected for some considerable time but only shows parasites in a certain proportion of examinations, represented by p.

If the first of these currently represented the happenings, Wilson's formula would be accurate. It would give the ultimate value of the parasite rate which would be reached at the end of time p would be unknown at about three months. The data in his own paper show that this does not occur. If the alternative meaning of p is accepted, his formula would represent the proportion affected at the end of one year of exposure. It does not state what would happen during the second year. To make the expression usable it would have to be amplified by a statement not only of the proportion of examinations on which an individual was positive, but also of the length of the period for which he continued to show positive blood films. On this second interpretation it shows the proportion positive at the end of one year, some having finally recovered in that time without subsequent later happenings.

The relation now found and described is radically different from Wilson's. The choice between the two must depend on an examination and an analysis of the conditions of the assumptions made, and whether they have been correctly interpreted into mathematical symbols, rather than on a study of the actual mathematical workings.

The theory is related to Chwatchatch's classical description of hyperendemic malaria. He noticed that there were areas in which the epidemiology of malaria differed in kind as well as degree from that in less malarious areas, being specially characterized by heavy and crowded transmission permanently in infancy, followed by the acquisition of immunity. It is now suggested that the hyperendemic areas are those in which the immunization rate exceeds the recovery rate so that a person once infected needs, not to recover, but to maintain his level of infection, so that the average individual suffers from parasitaemia due to several immunization infections. The p term of this mean overload can be estimated from the expression $L - \frac{k}{r}$. When one is considering the question whether parasitaemia is present or not, this must be taken as unity when k exceeds r, because as previously shown zero or negative recovery do not then occur. The higher value which could be considered has a real meaning and represents the average number to which parasitaemia is due to successive infections. For instance in the Bling series, the mean is estimated as 2·6, which means that the average level of infection carried is two and a half times as great as in a place where the immunization rate is the same as the recovery rate.

The present writer (Macdonald, 1950) has presented a theory of the mechanism of infection in endemic and hyperendemic conditions. This presumption was known to be deficient in that no element of time was introduced. It was stated that a certain number of bites would produce a certain number of infections, but the author then had no basis on which to state the time in which they would have to repeat to produce the given result. The present theory is larger. The previous one by assumption of the time element and by making proper allowance for superinfection. It can now be seen that the previous one was a very close relative of Wilson's recent theory and with similar assumptions.

The present writer also concluded in the previous paper that infection in the mosquito is chronic rather than continuous, infections occurring primarily at long intervals, although the observations were made in a hyperendemic area. The present work is built on this fact of mine as an assumption and is an elaboration of it. It does not assume the contrary but leads to the conclusion that it was correct, the frequency of infection in nature has been commonly exaggerated.

Field application

The present work consists of the presentation of a theory and its comparison with observed happenings and an enquiry into its applicability to malaria, which it is considered has been established. It was not intended as a purely academic study but as a means of re-opening the approach to some problems in malariology. There is much discussion at the present time on the nature of immunity which is observed in adult Africans of some races, opinions on the causation of which differ. Some consider that it is solely attributable to the load of infection which these people carry, and is a simple acquired immunity. Others consider that there is a strong racial element in it, the immunity being acquired much more readily in some races than in others though the load of infection may be lighter. The first object of this work was to facilitate the solution of this problem by making it possible to get a reliable estimate of the load of infection to which different groups of people are exposed, so that comparison with the amount of immunity acquired would be simplified. It is now suggested that the attack on this problem should be by the study of infant parasite rates, from which to estimate the inoculation rate; associated with this there should be an estimate of the amount of immunity acquired at different ages. This can be quite simply expressed numerically by examination of the parasite rate. At all ages past early childhood this parasite rate must be equal to the inoculation rate divided by the recovery rate. The decrease in the parasite rate with increasing age is attributable to an increasing recovery rate which in some areas or people finally approaches unity when the parasite rate becomes virtually nil. It is also hoped that the work will facilitate the direct measurement of the effects of malaria control measures as, for instance, by residual insecticides.

The children examined should all be under two years of age; it is essential that there should be a considerable number under one year old and it is possible to work with this group alone. Thick blood films should be taken, and it is suggested that 150 fields should be examined before a film is declared negative. The children should then be classed into age groups. It is preferable to have at least 50 in each group and ideal to have considerably more; the age groups used may, therefore, cover three months or less, depending on the number of infants examined. The parasite rate for each age group should be worked out and expressed as a proportion, not a percentage, according to which system, for instance, 0·32 is equivalent to 32 per cent.

These figures should then be recorded on a graph, to see whether they follow a regular curve of the type described. If they do not there may be some disturbing factor such as a very marked seasonal incidence of malaria which will involve special consideration. If they follow a reasonably regular curve they should be analysed in the following way: First examine the results, and if the parasite rate exceeds 0·9 (90 per cent.) in two or more age groups discard all findings after the first which does so. Then take each age group separately, refer to Table III and note the figure in the third column, which corresponds to it. Divide the parasite rate expressed as a proportion by this figure. This gives the value of L, which if below 1·0 is the ultimate value of the parasite rate which would be attained if the infants continued to be exposed in the future to the inoculation rate they have experienced in the past.

Each age group should be dealt with in this way, and the mean value of L then calculated. Subsequent working will differ according to whether this mean is above or below 1·0. If it is below 1·0, it should be multiplied by 0·005; the resulting figure is the inoculation rate or proportion of the population

receiving infective bites on an average day. If it is desired to work in percentages it should be multiplied by 100, which gives the percentage inoculated daily.

If the mean value of L found in this way exceeds 1·0 it gives no direct information on the inoculation rate, merely indicating that the latter exceeds the recovery rate, and that if the infants continue to be exposed to this degree of transmission their parasite rate will ultimately reach about 1·0 (or 100 per cent.). The figure must then be discarded and the individual age groups worked again in the following way.

First refer to Table IV, and choosing the value of x which is nearest to the parasite rate to be analysed, note the figure against it,* ignoring the negative sign. Thus if the parasite rate were 0·70 (70 per cent.) the figure noted would be 0·52288.

Then refer to Table III and note the value of $-0{\cdot}4343t$ corresponding to the age group. If the group was aged three, four and five months this would be $-55{\cdot}156$. The negative sign should again be ignored, as in working the two ultimately cancel each other out.

Divide the figure derived from Table IV by the second derived from Table III, producing in this case the result 0·0095. This is the inoculation rate necessary to produce a parasite rate of 0·70 in children aged 127 days (or in the age group three, four and five months).

This figure should be calculated for each age group and the mean taken as representing general conditions in the area studied.

When it is thought that transmission has remained materially unaltered over a period of two or three years, and the parasite rate does not reach a high level (for instance does not exceed 0·8) in any group, the inoculation rate may be simply derived from the parasite rate in children aged two to five years. This last figure expressed as a proportion should be multiplied by 0·005. If the parasite rate were 69 per cent. the calculation would be $0{\cdot}69 \times 0{\cdot}005 = 0{\cdot}00345$. This is the inoculation rate necessary to produce the given parasite rate. Care should be taken in using this simplified method to verify the fact that at no younger age does the parasite rate materially exceed the one worked on, or serious errors may result.

The theory has, up to the present, been applied solely to places where malaria is more or less perennial, as its application is clearly much simpler in them. Age distribution graphs in places where malaria is seasonal must clearly be discontinuous, but it should be possible to analyse them when this discontinuity is borne in mind and allowed for. The parasite rate in older children should attain a level which corresponds to the same formula as in the places where malaria is perennial, and its interpretation when it is well below unity (or 100 per cent.) should be simple.

Summary

Reference is made to a previously elaborated theory dealing with the relationship between inoculation rates and infection rates in those diseases in which superinfection can occur. The justice of the application of this theory to malaria is discussed with particular reference to the occurrence of superinfection. It is concluded that during the first couple of years of life in hyperendemic areas, and perhaps for longer periods in places of lower endemicity, superinfection can be considered a normal happening and the theory can justifiably be applied.

* It is, of course, better to work out log. $(1-x)$ for the exact figure to be analysed.

The recovery rate in untreated *P. falciparum* malaria is discussed on the basis of observed data. A general formula is deduced and compared with actual figures. It is concluded that the normal daily recovery rate is about 0·005.

Methods of direct measurement of the inoculation rate in malaria are discussed. It is concluded that though valuable evidence has been produced, the sources of potential error are considerable, and direct estimates only throw general light on actual happenings.

The mortality rate is briefly considered ; no effort is made to estimate it as it is noted that its effect on infection rates is immaterial.

On the basis of the previous work, formulae are given for :—

(*a*) The local recovery rate when account is taken of the probability that some potential recoveries are masked by infection.

(*b*) The ultimate value of the parasite rate. It is pointed out that this varies directly with the inoculation rate, and not indirectly as happens when superinfection is excluded, and as has commonly been considered the case in malariology. This is in direct contrast with common thought and teaching, and the modification suggested is thought to have important repercussions.

(*c*) The change in the rate with age. The formula given in this connexion makes it possible to analyse age incidence data, and to synthesize theoretical curves. Illustrative examples of the type of curves to be expected with different inoculation rates are given, and their characteristics are discussed.

The method of analysis of observed data is described and amplified by tables intended to simplify the use of mathematical formulae.

All the infant parasite rates recorded by ages from places where malaria is perennial, which are known to the author, are analysed ; the ultimate value of the parasite rate and the inoculation rate responsible are deduced. In each case theoretical curves have been built up based on these constants and compared with the actual curves. The comparison between observed and theoretical results is discussed, and it is concluded that the comparison demonstrates that :—

(*a*) the general type of formula used is correct, and

(*b*) the sole constant assumed in their analysis, the recovery rate, is reasonably applicable.

The possibility of a hereditary immunity having affected infant parasite rates in such a way as to upset the application of the theory is considered and rejected.

The relationship of present to past theories is briefly considered.

References

Barber, M. A. & Olinger, M. T. (1931) *Ann. Trop. Med. & Parasit.*, v. 25, 461. [*Trop. Dis. Bull.*, 1932, v. 29, 331.]

Blacklock, D. B. & Gordon, R. M. (1925) *Ann. Trop. Med. & Parasit.*, v. 19, 327. [*Trop. Dis. Bull.*, 1926, v. 23, 130.]

Christophers, S. R. (1924) *Indian J. Med. Res.*, v. 12, 273. [*Trop. Dis. Bull.*, 1925, v. 22, 396.]

Earle, W. C. (1939) *Puerto Rico J. Pub. Health & Trop. Med.*, v. 15, 3. [*Trop. Dis. Bull.* 1940, v. 37, 495.]

Earle, W. C., Pérez, M., Del Rio, J. & Arzola, C. (1939) *Puerto Rico J. Pub. Health. & Trop. Med.*, v. 14, 391. [*Trop. Dis. Bull.*, 1940, v. 37, 178.]

Garnham, P. C. C. (1949) *Ann. Trop. Med. & Parasit.*, v. 43, 47. [*Trop. Dis. Bull.*, 1949, v. 46, 1113.]

GORDON, R. M. & DAVEY, T. H. (1932) *Ann. Trop. Med. & Parasit.*, v. 26, 65. [*Trop. Dis. Bull.*, 1932, v. 29, 695.]

JAMES, S. P., NICOL, W. D., & SHUTE, P. G. (1932) *Proc. Roy. Soc. Med.*, v. 25, 1153. [*Trop. Dis. Bull.*, 1932, v. 29, 693.]

MACDONALD, G. (1931) *Indian J. Med. Res.*, v. 18, 1347. [*Trop. Dis. Bull.*, 1931, v. 28, 995.]

MACDONALD, G. (1950.) *Trop. Dis. Bull.*, v. 47, [above].

PUTNAM, P. (1931) *Ann. Trop. Med. & Parasit.*, v. 25, 502.

ROSS, R. (1916) *Proc. Roy. Soc.* Ser. A, v. 92, 204.

RUSSELL, B. A. S. (1938) *Trans. Roy. Soc. Trop. Med. & Hyg.*, v. 32, 237. [*Trop. Dis. Bull.*, 1939, v. 36, 130.]

WALTON, G. A. (1947) *Ann. Trop. Med. & Parasit.*, v. 41, 380. [*Trop. Dis. Bull.*, 1948, v. 45, 401.]

WALTON, G. A. (1949) *Ibid.*, v. 43, 117. [*Trop. Dis. Bull.*, 1950, v. 47, 208.]

WILSON, D. Bagster. (1936) *Trans. Roy. Soc. Trop. Med. & Hyg.*, v. 29, 583. [*Trop. Dis. Bull.*, 1936, v. 33, 765.]

SUMMARY OF RECENT ABSTRACTS*

VIII. TYPHUS GROUP OF FEVERS

General

A symposium on the Rickettsial Diseases of Man has been published by the American Association for the Advancement of Science (p. 590). The authors of the various papers are men whose names have been connected with research and control, and the original work (of 247 pages) should be studied in full; no abstract could do justice to it. The report of the First Inter-American Conference on Typhus is reviewed on p. 715. Most of the work recorded has been abstracted in this *Bulletin*.

In a note on fevers of the typhus group in the Sudan, PRATT *et al.* (p. 1021) show that records of these diseases are rare.

Various species of rickettsia were inoculated into ticks by WEYER (p. 624), who reports that in some cases, but not all, the strains became extracellular and non-pathogenic for mice during the process.

BOVARNICK and SNYDER (p. 927) have studied the respiration of typhus rickettsiae.

RIS and FOX (p. 928) describe the cytological structure of rickettsiae.

LODENKÄMPER (p. 129) shows that there was considerable difference between two strains of *Proteus OX19* used for the Weil-Felix test in Germany, in patients with fevers other than typhus. In typhus, however, the differences were not apparent. TRIFFTERER (p. 130) found a fairly uniform correlation between the Weil-Felix titres of sera from patients with typhus or other fevers, and the maximum dilution of glucolipoid from *Proteus X* which produced precipitation when added to the sera. LIU (p. 245) has investigated the Weil-Felix reaction in typhus and other fevers in China, and reports that the test was persistently negative in 6·6 per cent. of cases of typhus, and was positive at titres of 1 in 40 or more in 7·4 per cent. of the other fevers.

BARNES (p. 129) corroborates earlier findings by other workers that the Weil-Felix test with *Proteus OX19* is more often positive in pregnant than in non-pregnant women. CARRERE and MOUSTARDIER (p. 538) found a very high

*The information from which this series of summaries has been compiled is given in the abstracts which have appeared in the *Tropical Diseases Bulletin*, 1949, v. 46. References to the abstracts are given under the names of the authors quoted and the pages on which the abstracts are printed.

proportion of sera from pregnant women positive to the Weil-Felix test with *Proteus OX19*, by the slide agglutination method.

SMADEL (p. 453) has written a summary of his work on chloromycetin in fevers of the typhus group. SMADEL *et al.* (p. 626) have shown that synthetic chloramphenicol is as effective as the natural substance in the typhus group of fevers. SMADEL *et al.* (p. 1025) have carried out therapeutic tests with chloromycetin in various rickettsial infections of chick embryos and mice. Details of these experiments should be sought in the original.

HARDY (p. 725) reviews a number of papers on aureomycin, which is particularly indicated in the rickettsial diseases and certain other conditions. It is usually given by mouth in doses of 25–100 mgm. per kgm. daily for 5–14 days. Parenteral injections are reserved for severe infections.

FOX (p. 819) found that yolk-sac cultures of rickettsiae in water-in-oil emulsions provided particularly potent vaccines for certain rickettsiae and in certain animals, but not for all rickettsiae and all animals tested. FOX *et al.* (p. 819) have experimented in man with various forms of vaccine made from murine rickettsiae.

Proteus OX19 type: Vectors louse and flea

Louse typhus

Epidemiology.—Two cases of louse-borne typhus are reported by NEILL (p. 927) from Northern Ireland.

In a discussion of a laboratory outbreak in persons who had already had typhus, WEYER (p. 716) suggests that the disease may have been a late relapse (Brill's disease), or trench fever, or a mixture of the two. In certain conditions he thinks that *R. prowazeki* may be transformed into the extracellular form, *R. wolhynica*, and *vice versa*.

ERZIN (p. 343) gives an account of the incidence of typhus in Turkey before and during the war of 1939–45. There was a severe outbreak which lasted from 1942 to 1947, reaching a peak each year in spring; it was brought to an end by means of immunization and the use of DDT. Louse-borne typhus occurred in epidemic form in south-west Arabia in 1939–43, at altitudes of 4,000 feet and upwards (PETRIE, p. 1135).

FERRO-LUZZI (p. 344) shows that in Eritrea three forms of typhus are found, epidemic, murine and tick-borne, though the last is rare. During the war there were epidemics of louse-borne typhus, and the murine type occurred throughout. He treats his patients with aspirin given in quantities of 6–8 gm. daily, and claims good results. He suggests that the action of aspirin may be associated with the benzoic radicle.

As a result of complement-fixation and rickettsia agglutination tests on strains isolated in Urundi, JADIN (p. 22) concludes that they were mostly of epidemic type.

RIVOALEN (p. 23) refers to an outbreak of typhus in Tonking in 1944; it seems probable that it was epidemic typhus carried by lice.

Louse-borne typhus occurred in Japan in 1946, and EVANS (p. 23) makes the point that the murine type is also endemic there.

The first case of Brill's disease with serological pattern consistent with recrudescent epidemic typhus in Baltimore has been reported by SCHOENBACH (p. 539), who treated the patient successfully with aureomycin.

Complement-fixation tests indicate that the typhus of Peru is of the epidemic type (FREEMAN *et al.*, p. 537).

Aetiology, transmission.—WEYER (p. 623) discusses the great variation in virulence and habit of growth observed in rickettsiae of louse-borne and flea-borne typhus. The strains were maintained in various arthropods and animals.

Variations in one strain may be greater than the differences usually relied upon to distinguish one species from another.

A strain of *R. prowazeki* of low virulence was isolated in Spain in 1941. PEREZ GALLARDO and FOX (p. 24) have maintained it in eggs. The immunity it provokes in animals is weaker than that caused by other strains, but gives some protection, and the authors think that its use experimentally as a live vaccine would be justifiable.

Various fishes, apparently, can be infected with epidemic or murine rickettsiae (GIROUD and CIACCIO, p. 625).

FOX (p. 817) investigated the suitability of various animals for isolation of epidemic and murine strains of rickettsiae, and concludes that the cotton rat is the animal of choice, though for certain purposes mice and chick embryos are more suitable. He comments on the long period during which rickettsiae persist in the brain and kidney of infected cotton rats.

KRYNSKI and WOJCIECHOWSKA (p. 1022) record their observations on the varying degrees of virulence of *R. prowazeki* to lice.

SMART (p. 245) has published a new edition of his booklet on lice, which includes information on louse control measures.

Pathology, clinical findings.—A monograph on exanthematic typhus was published in 1944 by FONSECA and WOHLWILL (p. 1195) in Portugal, and contains a full description of the morbid anatomy of typhus.

ZALMAN *et al.* (p. 538) show that in typhus the blood urea is increased and chloride diminished ; the patient should be treated accordingly. The erythrocyte sedimentation rate is a useful indication of prognosis in typhus (ZAHARIA and BERNFELD, p. 539). The reticulocyte picture in typhus has been studied by ZAHARIA and DIMITRIU (p. 928), who show that these cells are reduced after the 4th day, returning to normal during convalescence. This is probably a sign of damage to the bone marrow.

The complications of typhus which affect the ear are discussed by MITTERMAIER (p. 625). They are relatively common.

COMBIESCO *et al.* (p. 928) show that in experimental typhus, removal of the spleen late after an attack sometimes obliterates immunity.

Tests.—LIU *et al.* (p. 24) have compared the Weil-Felix with the complement-fixation test in louse-borne typhus in China ; fairly high titres were reached with each test in most cases. A rise in titre also occurred in some cases of fevers due to other causes. In Peiping ZIA and CHANG (p. 346) found that the complement fixation test with epidemic antigen almost always gave higher titres than with the murine antigen. The disease, therefore, appears to be largely of epidemic type.

DREGUSS and FARKAS (p. 345) find that in louse-borne typhus the complement-fixation test becomes positive about two days earlier than the Weil-Felix test. They (p. 346) show that the complement fixation test is a reliable means of estimating the immunizing value of typhus vaccines.

D'IGNAZIO and CODELEONCINI (p. 25) have used the micro-agglutination test with suspensions of *R. prowazeki* in suspected cases of typhus. Special features of their technique are the use of very low dilutions and repetition of the test every 4 hours. They claim that early diagnosis can be made by these methods. TAMIYA *et al.* (p. 927) have discovered a partial antigen common to *Proteus OX19, R. prowazeki* and *R. mooseri.*

Treatment.—In discussing 118 cases of typhus treated in Paris, GILBERT (p. 717) makes the point that the case mortality rate in patients under 40 years of age was 4·5 per cent., and in those over that age it was 17 per cent.

PAYNE *et al.* (p. 131) obtained excellent results in the treatment of severe louse-borne typhus with chloromycetin. They gave 1·5 gm. by the mouth once each day for 2–3 days, and this dosage was as effective as a larger dosage

tried in the earlier cases. Intravenous injection of 0·2 gm. dissolved in 2 cc. propylene glycol, given very slowly 4–5 times each day (usually in addition to the oral administration) was also used. No toxic reactions were observed.

MORONES (p. 130) found that *p*-aminobenzoic acid was of no value in tabardillo, when given rather late in the course of the disease.

FRANK (p. 1023) shows that convalescent serum is effective in typhus if it is given before the rash appears.

BIELING (p. 1022) has produced in rabbits a serum which neutralizes typhus toxins.

GALLARDO and FOX (p. 451) have used a technique of inoculation of massive doses of epidemic and murine rickettsiae into the abdominal cavity, or the heart, of guineapigs. This produces severe infections, but not intoxication, and may be useful in the study of chemotherapy or serum neutralization tests.

WEYER (p. 537) shows that the louse can be used in chemotherapeutic tests since it tolerates intrarectal infection and administration of drugs, and the effect of drugs on rickettsial growth can be observed by examining stained smears of the gut.

Vaccination, control.—SNYDER *et al.* (p. 817) show that the number of viable rickettsiae in lice fed on typhus patients who had previously been vaccinated with the Cox vaccine were minute compared with the number in lice fed on unvaccinated patients. This indicates that vaccination would reduce sharply the development of an epidemic.

SERGENT *et al.* (p. 539) have used a single dose of a relatively concentrated killed vaccine in place of three doses of the usual vaccine, in Algeria, without producing ill effect.

COMBIESCO *et al.* (p. 929) have experimented in man with 3 vaccines of *R. prowazeki*, from yolk-sac, mouse-lung and dog-lung respectively. In relation to the Weil-Felix and dry-blood agglutination tests there was little difference between them. The Giroud test showed no correlation with the Weil-Felix test, which suggests that the protective antibodies are independent of the anti-*Proteus* agglutinins.

Experiments performed by GIROUD and CIACCIO (p. 539) suggest that alcohol treatment of infected rabbit lungs may be a suitable means of obtaining attenuated living vaccines. GIROUD *et al.* (p. 717) have prepared an antigen from the lungs of infected rabbits by treatment with methyl alcohol in the cold, and GIROUD and CIACCIO (p. 717) one by treating such lungs with horse serum. Each antigen appeared to provoke some degree of immunity in animals.

SERGENT *et al.* (p. 718) were concerned in the first trials of MYL and DDT in the dusting of clothing for control of typhus in Algeria in 1943. For the control of the disease they advocate vaccination (a single dose of a killed vaccine) and the use of insecticidal powders.

Flea typhus

Epidemiology, aetiology.—Typhus was found in rats caught in Catania (Sicily) by GRASSI-BERTAZZI (p. 131). Strains of murine typhus rickettsiae have been isolated by BALTAZARD and BAHMANYAR (p. 25) in rats at Abadan, Persian Gulf.

STOKER (p. 26) isolated rickettsiae (probably all murine) from rat brains, bandicoot brains, and fleas, in Poona. A number of rats and bandicoots gave positive complement-fixation reactions with murine antigen, but not with Rocky Mountain spotted fever antigen.

KE *et al.* (p. 26) failed to isolate any murine rickettsiae from a large number of rat-brains, and fleas, in Lanchow, China, and they think that murine typhus probably does not exist there.

Typhus of murine origin is relatively common in Western Australia, especially in the municipality of Perth and other Metropolitan areas (COOK, p. 346).

Various serological reactions were carried out on rats by VARELA *et al.* (p. 719), in Mexico City where 9·7 per cent. were positive to the complement fixation test with murine antigen. POMALES LEBRÓN *et al.* (p. 132) found positive results to the complement fixation and Weil-Felix reactions in a large proportion of rats, in part of Porto Rico where human cases of murine typhus had been occurring. Typhus of murine origin is common in Porto Rico. POMALES LEBRÓN (p. 245) reports that there has been a striking lack of correlation between the titres of the Weil-Felix and the complement-fixation reactions in many of the cases. Positive fixation tests were found in 54 per cent. of rats examined. Experiments suggested that infection is not commonly spread in rats by feeding on dead rats, and that infection of man by contamination of food by urine or faeces of infected rats is rare.

PEREIRA *et al.* (p. 1023) have found typhus in the rats of Rio de Janeiro.

MOOSER (p. 452) discusses the nomenclature of the rickettsia of murine typhus.

In Mexico the opinion has been held that typhus of murine type may become adapted to lice and be transmitted in this way. Serological studies by FREEMAN *et al.* (p. 536) do not support this view, or the view that there is any immunological relationship between the murine and classical types.

GREIFF and PINKERTON (p. 246) have found penicillin X more effective than penicillin G against murine rickettsiae growing in eggs.

WEYER (p. 818) shows that the mouse flea *Leptopsylla segnis* is susceptible to *R. mooseri*, to some strains of *R. prowazeki*, and to the rickettsia of Q fever. Intracellular strains of rickettsiae, virulent for mice, sometimes become extracellular and non-virulent after transfer through the flea and further transfer through lice. This may be an effect of mutation.

Tests, treatment.—BRICEÑO-IRAGORRY (p. 718) discusses the Weil-Felix reaction in typhus of murine origin ; he emphasizes the value of rising titres. RICKARD (p. 347) has performed the complement fixation test in typhus of murine origin in America. The average titre in persons attacked 1–2 years previously was 1 in 30, in those attacked 3–4 years previously it was 1 in 18.

SADUSK *et al.* (p. 246) show that although administration of *p*-aminobenzoic acid at the time of infection of guineapigs with murine typhus prevented the onset of symptoms, the animals developed immunity. DIAZ-RIVERA *et al.* (p. 452) treated cases of typhus of murine origin with *p*-aminobenzoic acid, using total amounts up to 219 gm. in some cases. Results were favourable.

Prompt and satisfactory response to aureomycin was shown by 5 patients with typhus of murine origin treated by RUIZ SANCHEZ and RUIZ SANCHEZ (p. 453).

A compound known as Pb 852 has been used by BOCK and KIKUTH (p. 540) in experimental murine typhus, with some success.

The nitro analogue of DDT, given by mouth to mice infected with murine typhus, showed some degree of curative power (FITZPATRICK, p. 453).

Control.—Although spraying with a water emulsion of DDT of walls and ceilings of farmhouses in America proved efficient in the control of rat fleas and mites, NICHOLSON *et al.* (p. 26) found it more costly than the spraying undertaken for malaria control, and they suggest a combined spraying and dusting technique, to serve both purposes.

Typhus of murine origin caused 5,338 known cases in Southern U.S.A. in 1944, but only about 2,200 in 1947. WILEY and FRITZ (p. 247) attribute this reduction largely to the practice of dusting with DDT the holes and haunts of rats. This causes a reduction by 80 per cent. of the number of *Xenopsylla cheopis* and other fleas on the rats, and also reduces other ectoparasites. Lasting

results are not to be expected without systematic action against rats. HILL and MORLAN (p. 347) have used 10 per cent. DDT powder for dusting rat runs and hiding places in part of Georgia where murine typhus is common. This produced a significant reduction in the number of human cases and in the numbers of rats showing positive complement-fixation reactions, and in the degree of infestation with rat fleas. Studies on the dusting of rat harbourages with 10 per cent. DDT in pyrophyllite show that significant reductions took place in the numbers of *X. cheopis* and *Leptopsylla segnis* (RANDOLPH *et al.*, p. 818). DENT *et al.* (p. 929) observed a high mortality rate in a colony of rats dusted with DDT, apparently as a result of DDT poisoning.

Proteus OXK type: Vector, mite

AUDY (p. 724) has written on the risk of scrub typhus in the fringe habitats of forest clearings in Malaya, where the mite vectors are very common. PHILIP *et al.* (p. 1135) note the types of country in Malaya in which scrub typhus was found, namely a rubber plantation overgrown by weeds, cleared jungle, and abandoned vegetable gardens. Rickettsiae were found in pools of *Trombicula deliensis* and *T. akamushi*, most found on wild rats (*Rattus r. argentiventer*). Volunteers were infected on exposure in infested areas.

Cases of murine and scrub typhus are recorded from Calcutta by CHAUDHURI and CHAKRAVARTI (p. 718). KRISHNAN *et al.* (p. 719) discuss a series of cases diagnosed as typhus in Calcutta, of which most were of the *Proteus OXK* type. The remainder were of murine origin, or were the *OX2* type. They (p. 721) state that the rainy season is the season of greatest prevalence, and of the greatest abundance of *Trombicula deliensis*. Most of the patients were connected with the scrub country or the fields, and 20 per cent. of *Rattus rattus* caught were infected with *R. orientalis*.

BROWNING and KALRA (p. 722) isolated strains of *R. orientalis* from rats, shrews, field mice and mites collected in an area between Assam and Burma where an outbreak of scrub typhus had occurred. A strain of rickettsia found to be immunologically identical with the rickettsia of Rocky Mountain fever was isolated from ticks. One of the authors had an attack of scrub typhus although he had previously been inoculated with the Fulton vaccine. They suggest that there may be immunological differences between strains and that vaccines should therefore be polyvalent, and frequently administered. WILLCOX (p. 133) discusses scrub typhus as he saw it in Assam and Burma in 1944. The case mortality rate was 8·3 per cent.

GISPEN *et al.* (p. 1024) report scrub typhus from the city of Batavia.

JONES and KING (p. 1024) record a case of scrub typhus from China, probably the first to be reported there.

From the serological examination of two patients in Togo, LE GAC (p. 348) concludes that they were suffering from a fever related to scrub typhus.

KOUWENAAR and ESSEVELD (p. 723), in a series of experiments on guineapigs in Sumatra, found that most strains of scrub-typhus rickettsiae were immunologically similar. Protective antibodies in serum, however, were difficult to demonstrate. The rickettsiae tended to persist, after the animal had recovered, especially in the spleen and the blood, and the immunity appeared to be of the type known as premunition, which depends on the presence of the infective agent.

A history of the Karp strain of *R. orientalis* is given by DERRICK and BROWN (p. 930).

AUDY (p. 247) has written an account of the mites concerned in the transmission of scrub typhus. KRISHNAN *et al.* (p. 721) have succeeded in breeding and maintaining *Trombicula deliensis* in the laboratory, and have transmitted *R. orientalis* from mouse to mouse by the bites of these mites. MEHTA (p. 820)

describes his method of rearing *Trombicula deliensis* in the laboratory. This mite is the probable vector of scrub typhus in the Simla hills. COCKINGS (p. 132) describes various methods which may be used for trapping mites of the genus *Trombicula* in the field or collecting them from rats or from soil. A method for rearing nymphs from engorged larvae is also described.

HARRISON (p. 245) has issued a key to the rats of Malaya.

HAYASHI and WATANABE (p. 1024) show that the blood of patients may be found infective up to 92 days after recovery from an attack of tsutsugamushi fever.

Continuing observations have led SMADEL *et al.* (p. 27) to reduce the dose of chloromycetin for scrub typhus to a total of 6 gm. given in the space of 24 hours. SMADEL *et al.* (p. 1136) tested the prophylactic effect of chloramphenicol in volunteers. There was definite suppressive action, similar to that of mepacrine in *P. vivax* malaria, and good therapeutic action for the actual attacks. Several volunteers were given vaccine before exposure to infection, but there was no evidence of any protective effect.

BAILEY *et al.* (p. 348) describe a method for preparing antigen or vaccine, which involves repeated differential centrifugation of homogenized yolk-sac cultures of scrub typhus rickettsiae.

The Scrub Typhus Research Unit, Kuala Lumpur (p. 723), has prepared a pamphlet on the prevention of scrub typhus. The measures to be taken include impregnation of clothing with dibutyl phthalate, spraying of dangerous areas with crude oil, and smearing the legs of labourers with the same oil, employing labourers who have recovered from the disease, and the use of benzene hexachloride dust at the rate of one pound per acre, under expert advice. CROSS and SNYDER (p. 540) tested 5 compounds which did not irritate or stain the skin, for their efficacy against mites. These substances were used to impregnate garments, and were tested against benzyl benzoate; several were more effective than the latter, in that they gave protection even after 7 washings.

Indeterminate type: Vector, tick

PLETZITY (p. 248) notes that Marseilles fever [presumably boutonneuse fever] transmitted by *Rhipicephalus sanguineus*, occurs in the Crimea. Other forms of tick typhus are carried in Russia by *Dermacentor nuttalli*, *Haemaphysalis concinna* and *D. silvarum*, and rickettsiae have been isolated from *D. marginatus* and *H. cinnabarina punctata*.

VALERO (p. 820) reports from Palestine a form of rickettsial fever which has certain resemblances to Rocky Mountain spotted fever.

MAUZÉ *et al.* (p. 249) report probable tick typhus from Guadeloupe.

VALLEJO-FREIRE (p. 134) describes the cultivation in eggs of the rickettsia of the Mexican type of Rocky Mountain spotted fever.

LACKMAN and PARKER (p. 353) have examined serologically the rickettsia of North Queensland tick typhus, and, unlike some previous observers, they find that it belongs to the Rocky Mountain spotted fever and boutonneuse fever group, but is not identical with any one member of that group.

COLLINS *et al.* (p. 821) report on the ticks (and their hosts) of Long Island; they include *Dermacentor variabilis*, the vector of Rocky Mountain spotted fever in eastern U.S.A.

VALLEJO-FREIRE (p. 134) has succeeded in transmitting Mexican spotted fever from guineapig to guineapig by the bite of *Amblyomma striatum*.

DE MAGALHÃES and ROCHA (p. 349) give reasons for thinking that goats and deer, which are susceptible to the tick-borne typhus of Brazil, may be natural reservoirs of that disease. They carried out Weil-Felix reactions on several other species of animals, but the results were variable. DE MAGALHÃES

and ROCHA (p. 725) state that they have demonstrated the rickettsia of the Brazilian form of Rocky Mountain spotted fever in the milk of an infected goat. They think that human and animal cases may occur as a result of ingestion of infected material.

RODRIGUES and TRAVASSOS (p. 349) found that the complement-fixation test (Bengtson) was strictly specific in the tick-borne typhus of San Paulo, with local antigen and Rocky Mountain fever antigen. The diseases are identical.

HARRELL and AIKAWA (p. 724) have studied the pathogenesis of circulatory failure in Rocky Mountain spotted fever, during which there is increased permeability of the capillaries, possibly connected with production of a histamine-like substance. Indiscriminate parenteral medication may be harmful if too much fluid is given, and protein should be supplied by mouth rather than by transfusions ; nevertheless, adequate quantities of fluid must be given, especially in the early stages.

The good effect of chloromycetin in Rocky Mountain spotted fever is shown by the experience of PINCOFFS *et al.*, who treated 15 patients. In most cases convalescence was established within 3 days. The adult oral dose was 0·5 gm. every 3 hours, until the rectal temperature had remained below 100°F. for 24 hours.

COOKE (p. 251) treated a case of Rocky Mountain spotted fever with aureomycin by mouth, 1·0 gm. every 6 hours for 48 hours, and then 0·5 gm. every 6 hours for 24 hours (a total of 10 gm.). The result was rapid improvement. HARRELL *et al.* (p. 350) also report favourably on aureomycin, in oral doses of 3–6 gm. daily. ROSS *et al.* (p. 350), used aureomycin with great success in the same disease. They gave it by the mouth for periods varying from 4½ to 9 days, during which time 2·3 to 16·3 gm. were given. Very good results in the treatment of South African tick typhus with relatively small doses of aureomycin are reported by GEAR and HARINGTON (p. 1025). A similar result is recorded by HILDICK-SMITH (p. 1137). ANIGSTEIN *et al.* (p. 725) confirm the fact that aureomycin is very effective in guineapigs with Rocky Mountain spotted fever. Intermittent treatment is as satisfactory as continuous treatment.

In 1947 WOODWARD and RABY (p. 249) treated patients with Rocky Mountain spotted fever with *p*-aminobenzoic acid, with considerable success. Most of the patients were children, and treatment was usually started early.

LACKMAN and PARKER (p. 252) state that Rocky Mountain fever vaccines prepared from yolk sacs and from tick tissue are about equal in immunizing power, but the protein in the yolk vaccine may provoke anaphylaxis.

The measures taken in Brazil to control tick-borne typhus are discussed by DE MAGALHÃES (p. 930).

ORTIZ MARIOTTI and CALDERÓN (p. 351) have used benzene hexachloride for the control of *Rhipicephalus sanguineus.*

Q fever

DYER (p. 726) has written a paper on the history and present status of Q fever.

STOKER (p. 454) reports three cases of Q fever in Great Britain. An explosive outbreak in a school for recruits in Switzerland is recorded by VISCHER (p. 454). The source was not discovered.

OLIPHANT and PARKER (p. 253) report three cases of laboratory infection with Q fever, but do not discuss the mode of infection. A case of infection in a laboratory worker studying Q fever in Panama is reported by DE RODANICHE and RODANICHE (p. 455). A laboratory outbreak, involving 9 persons definitely, and 4 others probably, is described by NAUCK and WEYER

(p. 626). The mode of infection was probably by inhalation of infected dust. The complement fixation test showed that all persons in a laboratory in Hamburg, who had handled *R. burneti*, became infected, and all except one were ill (LIPPELT and CASELITZ, p. 1026). Another laboratory outbreak, probably caused by inhalation of infected material, is described by COMBIESCO *et al.* (p. 931).

Outbreaks in Germany of an illness resembling influenza, with signs of atypical pneumonia, were found to be Q fever by HENI and GERMER (p. 351), who state that the only reliable method of diagnosis was the complement-fixation test. Most of the patients had been associated with cattle, and infection may have been contracted from inhalation of dust containing dried faeces of infected ticks, the drinking of infected milk, and inhalation of infected sputum droplets. The last method would best explain the explosive character of the outbreaks and the spread through whole families.

The first outbreak to be recognized in Rumania is described by COMBIESCO *et al.* (p. 627).

In investigations on Q fever in Greece, CAMINOPETROS (p. 28) found that various animals, including goats, were infected in nature. The milk of infected goats is infective, and remains so throughout lactation. The author suggests that although transmission to man may occur by inhalation of droplets of infective sputum, the common mode of acquisition is from milk. IMHAÜSER (p. 29) reports the isolation of a rickettsia-like agent from animals infected with sputum of patients with " virus pneumonia " in Greece and S.-E. Europe.

PAYZIN (p. 352) reports an outbreak in a Turkish village, and suspects that it may have been the result of inhalation of infected dust from wool. A non-explosive outbreak in Israel is reported by KLOPSTOCK *et al.* (p. 1026), who were unable to determine the mode of spread. Positive complement fixation tests to Q fever were found by ROSENKRANZ (p. 1137) in cases of atypical pneumonia in Israel. Titres ranged from 1/32 to 1/2054, and in some cases rose during the course of the disease. In this outbreak KOMAROV and GOLDSMIT (p. 1138) isolated a strain of *R. burneti*.

The first case of Q fever acquired in the eastern United States is reported by JANTON *et al.* (p. 455).

In an epidemiological study of 300 cases of Q fever in California, BECK *et al.* (p. 454) found that transmission (which occurred at all seasons) was associated with employment with live-stock, residence near a dairy or stock yard, or the use of raw milk. IRONS *et al.* (p. 726) show that 5 per cent. of slaughterhouse workers in a place in Texas have complement-fixing antibodies for Q fever, and confirm the finding of the rickettsiae in raw milk. Sheep and goats on a farm where a human case had occurred also showed complement-fixing antibodies. STRAUSS and SULKIN (p. 726) have also found complement-fixing antibodies in meat packers and others in Texas and other places. The fact that more positive results were obtained with sera positive for tests for syphilis than in those negative for those tests suggests that the reaction for Q fever with the American antigen used may not be always strictly specific. LENNETTE *et al.* (p. 1138) found positive complement fixation reactions for Q fever in 2·6 per cent. of cattle, 37·9 per cent. of sheep, and 43·6 per cent. of goats in one part of California. *R. burneti* was isolated from the milk of sheep and goats. The mode of transmission is not known, but the swallowing of infected milk and inhalation of infected dust are possibilities. Transmission by ticks must be very rare. In the United States SHEPARD (p. 456) has tested many cattle sera (sent for a brucellosis test) by the complement fixation reaction for Q fever. Most of the positive results were from western States. Two thirds of the sera tested gave positive rickettsia agglutination reactions at titres of 1 in 5 to 1 in 125 ; these are regarded as non-specific.

Experiments made by PARKER *et al.* (p. 135) suggest that lactating cows may be infected by the milk ducts with *Rickettsia burneti*; attempts at infection by various other routes were not successful.

JELLISON *et al.* (p. 353) slaughtered a cow while it was excreting *R. burneti* in the milk; the changes found in the organs were not specific. The only parts found, as a result of guineapig inoculation, to contain rickettsiae were the udder, a supramammary lymph node, and the lung (in one test only). JELLISON *et al.* (p. 455) found that butter made from the milk of cows with Q fever remained infective in the refrigerator for 41 days. HUEBNER *et al.* (p. 823) have found that *R. burneti* in milk is killed by high-temperature short-time pasteurization, but not always by the holder process. It is evident that more work is needed to determine safe methods for eliminating the risk of infection by milk.

Cases of Q fever have occurred in a laundry in which overalls, etc., from the Rocky Mountain Laboratory, Montana, were laundered (OLIPHANT *et al.*, p. 457).

BLANC and BRUNEAU (p. 822) have discovered natural infection of *Hyalomma mauritanicum* with Q fever in Algeria. JELLISON *et al.* (p. 252) have isolated strains of the rickettsia from the Argasid tick *Otobius megnini* in California. This is the first time that an Argasid tick has been found infected in nature, though *Ornithodorus moubata* and *O. hermsi* have been infected in the laboratory. Q fever could not be transmitted by *Aëdes aegypti*, or by house flies, in experiments carried out by PHILIP (p. 455), but the faeces of infected *Dermacentor andersoni* remained infective for over a year if dried, and in this state they were infective if placed in the nostrils, eyes or mouth of guineapigs. Emulsions of infected faeces or organs were infective if placed on the unbroken skin of animals.

NAUCK and WEYER (p. 541) have examined a strain of rickettsia from a case of Q fever in Greece. They have infected lice and fleas by intra-rectal injection, and ticks by intracoelomic inoculation; the infection persisted in all these, especially the ticks. A full study of the morphology of the rickettsiae was made.

WOLFE and KORNFELD (p. 931) show that if the quantitative complement fixation method is applied, certain differences between strains of *R. burneti*, apparent by the usual tests, cannot be detected.

DE RODANICHE (p. 252) claims experimental evidence in favour of some degree of cross-immunity between murine typhus and Q fever, in infected guineapigs, but in comment MEGAW suggests that the experimental findings hardly justify such a conclusion.

COMBIESCO and DUMITRESCO (p. 627) show that blood infected with *R. burneti*, and kept under sterile conditions at room temperature, remained infective for almost 300 days.

COMBIESCO *et al.* (p. 931) describe the lesions caused by *R. burneti* in guineapigs.

WOLFE and KORNFELD (p. 456) have reason to believe that the conglutination complement-absorption test is more sensitive and specific than the complement fixation test in Q fever.

The signs and symptoms of Q fever as seen in California are analysed by DENLINGER (p. 727). Details should be sought in the original abstract, but note may be taken of the finding of segmented or lobar consolidation in X-ray films of the chest, in 77 of 80 cases. Recovery was usually rapid and complete; no definite benefit was observed from treatment with penicillin, sulphonamides, streptomycin or *p*-aminobenzoic acid. WEGMANN (p. 1026) describes a case of encephalitis after Q fever. Very few fatal cases of Q fever have been reported, but PERRIN (p. 822) gives details of the post mortem findings in one. Details

should be sought in the original. BROWN *et al.* (p. 352) record a fatal case in California.

BOWER (p. 932) gives a description of Q fever in California, for which aureomycin is said to be specific.

Trench fever

WEYER (p. 627) states that in 47 of 146 cases *R. wolhynica* was isolated from lice fed on patients with trench fever. In some the diagnosis could not have been made on clinical grounds alone. Dried faeces of infected lice were still infective by intrarectal inoculation for body lice after storage for two and a half years.

Rickettsialpox

The only known natural vector of rickettsialpox is *Allodermanyssus sanguineus*, but PHILIP and HUGHES (p. 248) have shown that *Liponyssus bacoti* is capable of transmission under laboratory conditions. Similar experiments with *Dermacentor andersoni* were unsuccessful, though there is closer immunological relationship of this disease with Rocky Mountain spotted fever than with other rickettsial infections. *Charles Wilcocks*

MALARIA

SERGENT, Ed. Aphorismes de paludologie. [**Malariological Aphorisms.**] *Arch. Inst. Pasteur d'Algérie.* 1949, Dec., v. 27, No. 4, 289–303.

To summarize existing knowledge of the epidemiology and prevention of malaria in the space of 24 pages must have been a formidable task. This the author has accomplished in this paper, which was written for the jubilee of Professor Enrique Beltran of Mexico.

The paper, for the most part, takes the form of classified synoptic paragraphs, often giving in the compass of a single sentence the main point under discussion. As a means of quick reference, or to provide " headlines " for an introductory or a revisionary study, it should prove admirable. *Norman White*

MARA, L. Studio sull'epidemiologia malarica del comprensorio agricolo di Tessenei. [**Malaria Epidemiology in the Tessenei Agricultural Development Area.**] *Riv. di Malariologia.* 1950, Feb., v. 29, No. 1, 1–49, 14 figs., 2 maps & 10 graphs. English summary.

Tessenei, an area in the west of Eritrea near the frontier of the Anglo-Egyptian Sudan, was selected for an intensive agricultural development project, involving irrigation work on a large scale. The area lies along the southern bank of the Gash River. In order to determine the effect of such work on the malaria endemicity of the region systematic observations were started in 1939 and continued with some intermission till the end of 1945. This report records the findings. Regular search was made for larval and adult anophelines in Ali Ghidir in the middle of the irrigated area, in Sabot, the administrative headquarters, which lies immediately to the west of the area, and in two other places in the western province which are unaffected by the scheme, Cheru and Gullui.

In Ali Ghidir the following species were encountered, *A. gambiae*, *A. pharoensis*, *A. rufipes*, *A. squamosus*, and *A. coustani* : in Sabot, *A. gambiae*, *A. dthali*, *A. rupicolus*, *A. pretoriensis*, *A. pharoensis* and *A. turkhudi*. In both places

A. gambiae is the main vector. *Plasmodium falciparum* is much the most prevalent parasite in all four localities. *P. malariae* was only exceptionally seen.

Irrigation in the agricultural experimental area has greatly increased anopheline breeding potentialities. At the same time it has greatly increased the economic and social wellbeing of the population. *Norman White*

GEUKENS. Notes au sujet du paludisme endémique au territoire de Feshi (Kwango). [**Notes on Endemic Malaria in the Feshi Territory, Kwango.**] *Ann. Soc. Belge de Méd. Trop.* 1950, Mar. 31, v. 30, No. 1, 31–46, 3 maps.

The author publishes notes concerning malaria endemicity in two regions inhabited by Africans of the Basuku tribe, where the soil is little productive, where scarcity is rife and where the natural increase of population is very small.

The Muzengo centre lies between the Inzia and Luie rivers. The observations recorded were confined to Africans living along the banks of the Luie River, about 5°40′ S. and 17°45′ E. The left bank of the river, where the majority of the population live, is marshy. According to "Foreami" reports the mortality rate of infants aged 0 to 3 years, in the area of which the Muzengo Centre forms two-fifths, is 152 per thousand. The blood of 100 infants from 0 to 3 years was examined. *P. falciparum* was found in 86; it was associated with *P. malariae* in 17. *P. vivax* was not found. The splenic index was 53·5 per cent. for infants 0 to 1, and 83 per cent. for infants 1 to 3 years. There was no difference in the parasite rates of the two age groups of infants.

In the Bumba Centre the population examined live along the banks of the Mwana Lukula, one of the two river sources of the Lukula, situated about 5°60′ S. and 18°5′ E. Here the infant mortality rate approximates 165 per thousand live births. Ninety infants aged 0 to 3 years were examined. The parasite rate for infants from 0 to 1 year was 70 and from 1 to 3 years 83·6 per cent. *P. malariae* was more frequent in the older group. Both *P. falciparum* and *P. malariae* were found in all the six villages investigated. *P. malariae* was found only nine times alone, and 16 times in association with *P. falciparum*. *P. vivax* was not seen. *Norman White*

HENDERSON, J. M. **Comments on Man-made Malaria in India.** *Indian J. Malariology.* 1949, June–Sept., v. 3, Nos. 2/3, 253–9.

A majority of the anopheline breeding places created by man in India are related to irrigation systems, borrowpits along railroads and highways, and obstructions to natural drainage. Seepages from water channels give rise to more prolific breeding than do the wet fields themselves. In surface irrigation systems the location of pits adjoining the embankments ensures the impounding of water that leaks from the water channel. The absence of silt tanks at the headworks has caused extensive silting in canals: this entails raising of embankment walls with consequent increase of borrowpits, and leakage increases with each successive lifting of the channel flow section above adjoining ground levels.

The recent trend in India towards the mechanization of earth moving practices will if continued avoid the creation of such hazards. There is, too, a developing interest in lining irrigation channels with concrete or soil cements. A substantial part of the added cost is recovered by savings in excavation and fill due to smoother flow sections. Intermittent perennial irrigation has given good results in curbing mosquito breeding but it is not everywhere applicable.

Borrowpits along highways can often be drained by breaking through the thin walls separating adjacent pits. This simple procedure is commonly neglected : it should be rigidly enforced.

The civil engineering profession in India has a major potential rôle to play in preventing and abating malaria. A thorough grounding in the rudiments of malaria control engineering is an essential part of the undergraduate training of every civil engineer regardless of specialized interest. Such training should be provided by a qualified resident faculty member at every college of engineering in India. Moreover, the training, attraction and utilization of malaria control engineers within the health services, as active and responsible components of the medical-engineer-entomologist team, might achieve much.

Norman White

VENKAT RAO, V. **Malaria in Orissa.** *Indian J. Malariology.* 1949, June–Sept., v. 3, Nos. 2/3, 151–63. [30 refs.]

The province of Orissa was enlarged in size by the fusion of a number of feudatory states after India became independent. It now covers an area of nearly 60,000 square miles and has a population of 13,774,668. The hilly parts of the province have long been notorious for severe malaria, but the plains and coastal belt appear to have been relatively free from malaria in the latter half of the last century. Much has been published about the epidemiology of malaria in parts of Orissa, notably by Senior WHITE and his colleagues. In the hills there are three malaria vectors, *Anopheles fluviatilis*, *A. varuna* and *A. minimus* : in the plains *A. annularis* : along the coast *A. sundaicus*. In the hills, malaria is hyperendemic and transmission takes place at all seasons : the incidence curve has two peaks, the October–November peak being always higher than the March–April peak. In the plains, epidemics of malaria occur at intervals of four to six years : transmission is limited to the autumn. Along the coast there are endemic and hyperendemic areas.

In 1943, a severe epidemic of malaria in Berhampur was attributable to *A. sundaicus*, which was found breeding in overgrown fresh-water tanks. Berhampur is ten miles from the sea. Very high infection rates were found among the fresh-water strain of *A. sundaicus*, much higher than any found among salt-water strains.

A. annularis elsewhere than in the plains of Orissa is of negligible importance as a vector of malaria. It must be present in very large numbers to insure effective transmission. This is accounted for in the plains of Orissa by prolific breeding in rice-fields. DDT residual spraying offers the best hope of effective malaria control.

In the hill tracts which cover more than half the area of Orissa, and where malaria transmission is effected by anophelines of the fluviatilis group, the control of malaria by antilarval measures is impracticable. The population is scarce and poor. The aboriginal tribes which compose the greater part of that population have acquired a high degree of immunity. Here, too, DDT residual spraying of dwellings would appear to be the most economical method of control.

Much of the information contained in this paper has been previously published and noted in this *Bulletin*.

Norman White

GODBOLE, S. H., RAMACHANDRA RAO, T. & VISWANATHAN, D. K. **Malaria Survey of Bijapur District.** [Abstract.] *Indian J. Malariology.* 1948, Sept., v. 2, No. 3, 213–14.

SUBRAMANIAM, H. & CHETTY, K. N. **Malaria in Tirumalai Village, Chittoor District, Madras Presidency.** [Abstract.] *Indian J. Malariology.* 1949, June–Sept., v. 3, Nos. 2/3, 261–2.

LACHMAJER, J. **Studies on the Ecology of Mosquitoes of the Genus Anopheles in Szczecin (23. V–15. VI. 1949).** *Bull. Inst. Marine & Trop. Med., Med. Acad., Gdańsk, Poland.* 1949, v. 2, Nos. 3/4, 235–42, 3 graphs.

The anopheline mosquitoes found by the author in Szczecin, Poland, during May and June, 1949 were *Anopheles maculipennis maculipennis*, *A. m. messeae* and *A. claviger* ; sixty kilometres further north *A. m. atroparvus* also occurred.

Larvae of *A. maculipennis* were found in Szczecin in standing water in ponds, ditches, bomb craters, etc. Larvae of *A. claviger* were found in collections having an inflow of fresh water. Large overgrown swamps did not produce any larvae of *Anopheles*.

Adult *Anopheles* were very numerous in cowsheds ; the author estimated 2,000 to 5,000 mosquitoes for every shed. In unoccupied buildings a few anophelines were seen and out of doors they were rarer still, most of those caught being males.

The majority of the *A. maculipennis* were of the race *messeae* which was distinctly zoophilic and of no particular importance in relation to malaria transmission in normal times.

During the first post-war years the incidence of malaria had been augmented by new carriers coming to the city until by 1947 there were several hundreds of cases every year ; but with the cessation of the movement of people into the city, the simultaneous increase in the number of cattle in the neighbourhood and the introduction of more efficient anopheline control measures the number of cases was so reduced that between January and May, 1948, only three cases were recorded and these were traced to infection from the previous autumn.

H. S. Leeson

BRUCE-CHWATT, L. J. **Recent Studies on Insect Vectors of Yellow Fever and Malaria in British West Africa.** *J. Trop. Med. & Hyg.* 1950, Apr., v. 53, No. 4, 71–9. [27 refs.]

The investigations into jungle yellow fever made in Nigeria seem to provide growing evidence that the problems are different from those in East Africa because of the difference in the behaviour of the respective species of mosquitoes. In spite of much work done on *Aëdes africanus*, *Aëdes pseudoafricanus* and *Aëdes simpsoni*, the insect responsible for the transmission of West African jungle yellow fever has not yet been incriminated.

New lines of research into mosquito behaviour have been opened up through the development of the technique of recording mosquito sounds. One experiment with *Aëdes africanus* showed that this species remained inactive during the day but became active at dusk just at the time when the peak biting period occurs in nature.

The author also comments on the new method of marking adult mosquitoes by adding soluble salts of radioactive phosphorus or strontium to the rearing water. The salts which remain in the adult mosquitoes bred from the treated larvae can be detected by using a suitable Geiger-Müller counter.

Adults of *Aëdes aegypti* produced under these conditions were released and then recaptured daily for a month in an experimental area of over 12 acres. The maximum distance of recovery of radioactive specimens was 3,800 feet from the point of release.

A review of recent work on malaria vectors is also given. Seven species of *Anopheles* have been found naturally infected with the plasmodium of malaria in West Africa : *Anopheles gambiae* (including *A. gambiae melas*), *A. funestus*, *A. hargreavesi*, *A. pharoensis*, *A. nili*, *A. moucheti* var. *nigeriensis* and *A. hancocki*. *A. rufipes* has been found infected at Kano. Recent work

on cross-breeding showed that interbreeding of *A. gambiae* and *A. melas* is not difficult, that hybrid males are not sterile but that females mated with homologous males laid eggs all of which failed to hatch.

A. gambiae seems to be a more efficient vector of *Plasmodium falciparum* than is *A. melas* though the latter is specially important along the coast of West Africa. [This paper is a useful summary of the situation to date ; most of the papers referred to have been abstracted in this *Bulletin*.]

H. S. Leeson

BHATT, H. R. **A Note on a Natural Occurrence of Sporozoites of Plasmodium in *Anopheles turkhudi* Liston.** *Indian J. Malariology.* 1949, Mar., v. 3, No. 1, 109–10.

"A natural occurrence of sporozoites of plasmodium probably of avian origin is recorded in a specimen of *Anopheles turkhudi* from Nasik District."

HSU, S. C., FENG, L. P. & CHANG, T. L. **Observations on the Longevity of *Anopheles hyrcanus* var. *sinensis*.** *Chinese Med. J.* Shanghai. 1949, Sept., v. 67, No. 9, 491–5, 1 fig.

"A laboratory study [at Chungking in 1944] of the longevity of *Anopheles hyrcanus* var. *sinensis* brought out the following points :

"1. The average life span and mean temperature were closely correlated ; the lower the temperature within the range studied, the longer the life span. At a temperature threshold of about 26°C., mosquito mortality became very high. Although no observations were made at low temperatures, the adult density of *sinensis* dropped suddenly when the mean minimum fell to about 15°C.

"2. Relative humidity did not appear to have much effect when the temperature was favorable, between about 15°C. and 26°C., probably because the relative humidity in Chungking is usually within the favorable range, from 56 to 93 per cent. At the higher temperatures, however, it appeared that a high relative humidity increased longevity.

"3. Although in the period May–June, the temperature is favorable both for *Anopheles* and the development of malaria parasites in the mosquito, the interval is believed to be too brief to be important in malaria transmission. September and the early part of October, assuming that the weather is not too dry, are probably important months for *sinensis* as a vector since the favorable temperature remains fairly constant for the necessary length of time."

BELLAMY, R. E. **An Unusual Winter Population of *Anopheles quadrimaculatus* Say.** *J. National Malaria Soc.* 1950, Mar., v. 9, No. 1, 80–83, 1 fig. [11 refs.]

Weekly counts were made during the winter months December 1948 to March 1949 of the males and females of *Anopheles quadrimaculatus* resting in artificial shelters around three ponds in Georgia, U.S.A. Representative specimens were collected from time to time to confirm the identification. The minimum and maximum weekly numbers were respectively 4 and 250 males and 47 and 376 females.

This unusually large and persistent population is interpreted as being due to the abnormally warm winter of 1948–49 which had the highest mean daily temperature and the highest mean minimum temperature for 20 years. Weekly collections of larvae from the adjacent ponds suggested that *A. quadrimaculatus* adults emerged each month but not each week of the winter. *H. S. Leeson*

FROST, S. W. **Results of the Pennsylvania Mosquito Survey for 1948.** *Mosquito News.* 1950, June, v. 10, No. 2, 65–8.

"The operation of light traps throughout Pennsylvania for two consecutive years and additional mosquito studies make it possible to draw some general conclusions. *Culex pipiens* Linn., and *Aedes vexans* (Meig.) are the most common and widely distributed species in Pennsylvania occurring from early spring to late fall. *Uranotaenia sapphirina* (O.S.) occurs generally throughout the State but is seldom common and is not an important species. *Culex restuans* Theobald is another common and widely distributed species. Certain species are common only where proper breeding conditions exist. *Anopheles crucians* Wied. is common only in the eastern part of the State. *Anopheles walkeri* Theobald is abundant only at Presque Isle. It is very evident that *Mansonia perturbans* Walk. predominates at Philipsburg although it occurs to some extent at Presque Isle. *Anopheles quadrimaculatus* Say has been taken in small numbers from seven widely separated parts of the State."

BELLAMY, R. E. & REPASS, R. P. **Notes on the Ova of** *Anopheles georgianus* **King.** *J. National Malaria Soc.* 1950, Mar., v. 9, No. 1, 84–8, 3 figs.

The authors first point out that in volume two of HOWARD, DYAR and KNAB's monograph (1913–17) the figure of the egg of *Anopheles crucians* is labelled *A. punctipennis* and that of *A. punctipennis* is designated *A. crucians* and that the error has been perpetuated by subsequent authors. There is therefore some confusion in the literature as to the ova of *A. crucians.*

In South Georgia, U.S.A., the ova of *A. crucians* and *A. georgianus* were studied. A table of measurements of a small series of eggs of these two anophelines is presented. The figures provide no criterion by which they may be distinguished but as the fourth-stage larvae are recognizable it is assumed that *A. crucians* and *A. georgianus* are biologically distinct and separate species. *H. S. Leeson*

DE ZULUETA, J. **A Study of the Habits of the Adult Mosquitoes dwelling in the Savannas of Eastern Colombia.** *Amer. J. Trop. Med.* 1950, Mar., v. 30, No. 2, 325–39, 5 figs.

The author undertook the study of the behaviour of adult mosquitoes in their natural environment and found that the grassy plainland of Eastern Colombia was the true habitat of several species of culicines and at least three species of anophelines. In the daytime mosquito activity was absent but at night the mosquitoes mated and went in search of food.

A square covered muslin tent was erected which covered an area of ground of four square metres. Two men entered the tent and sprayed the inside with a repellent. All the disturbed mosquitoes were captured and kept for identification and study. The whole procedure took no more than twenty minutes with three men and fifteen minutes with four and captures were made every 100 metres. To collect flying mosquitoes at night large nets on poles were fixed to a motor truck which travelled over the savanna at 30 kilometres per hour. Stable traps were also used.

A total of 104 tent captures provided 1,234 mosquitoes ; of these 570 were male culicines and 536 were females ; there were 30 male anophelines and 98 females. The total mosquito density was estimated to be 3,000,000 mosquitoes per square kilometre of which 300,000 would be anophelines. These captures showed that *Anopheles peryassui, A. pessoai* and *A. parvus* live entirely in the savannas.

Female mosquito density was found to be approximately equal over the whole area but male density was greater near breeding places. No place was more than 1,800 metres from a breeding place but it is to be noted that the observations were made in the rainy season.

The author believes this tent method of sampling mosquitoes living in grass country is the most accurate he has so far tried. Captures on the wing are more rapid but less reliable and the stable traps cannot give true information about mosquito density in a given area. *H. S. Leeson*

MAEGRAITH, B. G., JONES, E. S. & SCULTHORPE, H. H. **Pathological Processes in Disease. I. Adaptation of the Warburg Respirometer for the Determination of Blood Gases.** *Ann. Trop. Med. & Parasit.* 1950, Apr., v. 44, No. 1, 101–6, 3 text figs. & 3 figs. on 1 pl. [10 refs.]

The method utilizes the principles of the Warburg manometric technique and the ferricyanide method of blood-gas analysis (COURTICE & DOUGLAS, *J. Physiology*, 1947, v. 105, 345). Blood samples of 0·3–0·6 ml. are used for each determination of blood gases (oxygen and carbon dioxide). The advantages of this technique, which is fully described, are simplicity and speed. A specimen oxyhaemoglobin dissociation curve of normal human blood as determined by the method is given. *J. H. Birkinshaw*

MUKHERJEE, S. K. & MITRA, A. K. *Plasmodium vivax* **Infection.** [Memoranda.] *Brit. Med. J.* 1950, July 8, 88–9.

This paper relates to a Hindu student of 33 in Calcutta, who suffered from four attacks of severe abdominal colic within 10 days : the second and third attacks were accompanied by widespread urticaria. Fever between 102° and 103°F. also occurred. The attacks of colic usually subsided within a few hours.

There was no dietetic evidence to explain the urticarial attack and no pathological condition in the stool which would account for the colic. Antistin, given in addition to general treatment, prevented recurrence of the urticaria, but not the colic and fever which occurred without urticaria in the fourth attack. At this stage trophozoites of *Plasmodium vivax* were found in moderate numbers in blood films. The patient was treated with proguanil and the attacks did not recur.

The authors suggest the presence of a " unitary nature of the symptom-complex " and note that symptoms disappeared completely after proguanil treatment, while antistin did not prevent return of the colic and fever. It is pointed out that abdominal pain is a common manifestation of *P. falciparum* infections. In this case the classical initial clinical features of malaria were absent, *e.g.*, chill, rigor, nausea, vomiting, profuse sweating during defervescence. [This case has certain features in common with that reported by MOHAPATRA, this *Bulletin*, 1950, v. 47, 316.] *H. J. O'D. Burke-Gaffney*

NICOLLE, Marcelle. Maladies exotiques des nouveau-nés. [**Tropical Diseases in Newly-Born Infants.**] *Semaine des Hôpit. de Paris.* 1949, June 26, v. 25, No. 47, 2031–6.

The author's attention is confined to parasitic diseases affecting the newly born, infection with which may be transmitted from parent to offspring before birth. It is this transplacental method of disease transmission which is considered at greatest length. Most attention is devoted to congenital malaria and to malaria acquired during the first few days of life. Toxoplasmosis and the

trypanosomiases are also considered. The symptomatology, diagnosis and treatment of neonatal malaria are well described. Transplacental transmission of malaria, although it is rare, undoubtedly occurs. *Norman White*

TRUONG-VAN-QUE. Paludisme et métrorragies. [**Malaria and Metrorrhagia.**] *Rev. Méd. Française d'Extrême-Orient.* 1942, June–July, v. 20, No. 6, 840–41.

Report of a case.

HANDFIELD-JONES, R. P. C. **Chloroquine, Proguanil, Mepacrine and Quinine in the Treatment of Malaria caused by** *Plasmodium falciparum.* *Ann. Trop. Med. & Parasit.* 1949, Dec., v. 43, Nos. 3/4, 345–8.

In the latter half of 1948 there was an epidemic of *P. falciparum* malaria in an army garrison at Mackinnon Road in Kenya, 70 miles inland from Mombasa. Sixty uncomplicated cases were treated with one or other of the four drugs listed in the title, 15 with each. Cases of cerebral malaria were excluded, as were mild cases in which the temperature did not exceed 100°F.; otherwise there was no selection. Thick blood smears and temperatures were taken of each patient every four hours. The dosage was as follows:—

Chloroquine diphosphate: initial dose, 1·0 gm. [0·6 gm. of base] followed after six hours by 0·5 gm. The 0·5 gm. dose was repeated on the second and third days. Total dosage 2·5 gm. (1·5 gm. of base).

Proguanil: 0·1 gm. thrice daily for seven days. Total dosage 2·1 gm.

Mepacrine: 0·4 gm. thrice on the first day; 0·3 gm. thrice daily on the second and third days; 0·1 gm. thrice daily on fourth, fifth and sixth days. Total dosage 3·9 gm.

Quinine sulphate: 0·66 gm. thrice daily for five days. Total dosage 9·9 gm. in solution.

All the drugs were given by mouth. After treatment all patients received the standard suppressive dose of mepacrine 0·1 gm. a day. Towards the end of the study this was changed to the same dose of proguanil.

The duration of fever was shortest with chloroquine; one patient so treated was afebrile in 20 hours and none had fever for more than 80 hours. Mepacrine was the next most active in lowering the temperature. Chloroquine also caused the disappearance of parasites from the peripheral blood more rapidly than did the other three drugs. Parasites persisted for more than 24 hours in only 3 of the 15 patients treated with chloroquine as compared with 5 with proguanil, 7 with mepacrine and 5 with quinine.

The author found that the East African strain of *P. falciparum* responds readily to proguanil and that "there is no necessity to combine with proguanil other schizonticides such as mepacrine, as was advised by COVELL from experience with the Lagos strain." [The chief reason why Covell [this *Bulletin*, 1950, v. 47, 11] recommended reinforcement of proguanil with mepacrine was that proguanil unaided did not effect radical cure; short-term recrudescences occurred in a number of cases. In the series here reported the patients were given suppressive mepacrine or proguanil daily, immediately after the completion of the therapeutic course. This might explain the absence of recrudescence. The observations afford no evidence that the Lagos strain is more resistant to proguanil than the East African strain of *P. falciparum*.]

Norman White

BRUCE-CHWATT, L. J. & BRUCE-CHWATT, Joan M. **Antimalarial Drugs in West Africa, with particular reference to Proguanil. Results of a Survey in Nigeria.** *Brit. Med. J.* 1950 (July 1) 7–14. [27 refs.]

In an attempt to assess the comparative value of different antimalarial drugs in the prophylaxis and treatment of malaria in West Africa, two questionnaires were circulated, one in August 1949 to 315 medical officers in Nigeria and the other in October 1949 to 1,400 non-African householders in Lagos, representing about 70 per cent. of the non-indigenous population. Replies were received from 40 per cent. of the medical officers and from 46 per cent. of the non-African residents.

The prophylactic efficacy of the various drugs could not be assessed with accuracy for a variety of reasons. There is a turnover of about 30 per cent. of the European population each year, and relatively few return to the same station after completing an 18-month's tour. Medical facilities vary considerably in different stations, and records lack continuity owing to frequent changes of station medical officers. Moreover, the standard of laboratory technique for the diagnosis of malaria is often inadequate. Another source of error is that some medical officers record as malaria all cases where the clinical picture suggests that this may be the cause, whereas others list under this heading only those cases where parasites have actually been seen in a blood smear. The mean overall ratio of "clinical malaria" to "blood-positive malaria" in Nigeria is 2·5 : 1 in Europeans. All cases designated as malaria by medical officers were classed as such in the survey under review.

For the prophylaxis of malaria, proguanil is the drug most widely used among the non-African population. The figures reported in the survey were 65 per cent. taking proguanil, 22·5 per cent. quinine, 10·5 per cent. mepacrine and 0·9 per cent. chloroquine. Of those taking proguanil, 87 per cent. were on a dosage of 0·1 gm. daily. The usual dosage of quinine was 5 grains daily and that of mepacrine 0·1 gm. three to seven times weekly. The chloroquine group included 34 individuals only, the dosage being 0·5 gm. of the salt weekly.

According to medical records, overt malarial attacks occurred in 9·9 per cent. of those on proguanil prophylaxis; in 23·6 per cent. of those on quinine; in 20·6 per cent. of those on mepacrine; and in 23·5 per cent. of those on chloroquine. The corresponding figures resulting from the questionnaire issued to householders in Lagos were 10 per cent. for proguanil, 19 per cent. for quinine, 24·8 per cent. for mepacrine and 16·6 per cent. for chloroquine. The proportion in each category who actually took the prescribed drug with unfailing regularity must remain a matter for speculation.

The authors endorse the view expressed by the majority of medical officers from whom replies were received that proguanil taken in a daily dose of 0·1 gm. is superior both to mepacrine and to quinine as a prophylactic. Commenting on the large proportion of "break-throughs" even in the proguanil series, they admit that some of these may be due to errors of diagnosis or failure to take the drug regularly, but note that several cases occurred among persons vouched for as regular takers of the drug by conscientious and experienced medical officers, and consider that these cannot be lightly disregarded.

With regard to the therapeutic value of proguanil, the consensus of medical opinion in Nigeria confirms previous findings as to the comparatively slow action of this drug and its failure to effect radical cure of West African *P. falciparum* malaria when given unaided [this *Bulletin*, 1946, v. 46, 825]. For the emergency treatment of *P. falciparum* infections characterized by hyperpyrexia, cerebral symptoms, persistent vomiting and massive parasitaemia, quinine given intravenously or intramuscularly is still the most favoured drug.

For treatment of the average malarial attack, the systems preferred by the medical officers who replied to the questionary were :—

Mepacrine only	27
Quinine only	18
Proguanil only	8
Chloroquine only	1
Mepacrine plus quinine	24
Proguanil plus quinine	**23**
Proguanil plus mepacrine	**13**

The authors note that data relating to chloroquine are as yet meagre, but the few available medical reports as to its therapeutic value in West Africa indicate that this is probably the most powerful synthetic schizonticide yet produced, achieving radical cure of a high proportion of *P. falciparum* infections with very few objectionable side-effects. *G. Covell*

DURAND, P., SCHNEIDER, J. & DUPOUX, R. Traitement en un jour de l'accès de paludisme par la nivaquine. [**One Day Treatment of Malaria Attacks with Nivaquine [Chloroquine].**] *Bull. Soc. Path. Exot.* 1949, v. 42, Nos. 11/12, 549–54.

The remarkable antimalarial activity of nivaquine [chloroquine], the absence of symptoms of intolerance even when the drug is administered in doses much higher than those usually employed, and the fact that the drug is accumulated in and only slowly eliminated from the organism, prompted the choice of nivaquine in the search for an effective one-day treatment for acute attacks of malaria.

Ninety-five patients were treated in two hospitals in Tunisia. Of these, 59 patients (37 *P. falciparum*, 19 *P. vivax*, 2 *P. malariae* and 1 *P. falciparum* and *P. vivax*) were each given two doses of 0·6 gm. of nivaquine at an interval of 12 hours.

Sixteen patients (10 *P. falciparum* and 6 *P. vivax*) were each given the same doses separated by an interval of 24 hours.

Nineteen patients (11 *P. falciparum*, 6 *P. vivax* and 2 *P. malariae*) were treated with a single dose of 0·6 gm.

An infant weighing 10 kgm. was given a single dose of 0·2 gm.

The results were good. There was little to choose between the first two methods of treatment. Preference is given to the 12-hour interval between the doses as this method does not necessitate the admission of the patient to hospital. The results with a single dose of 0·6 gm. were not quite so prompt but the authors consider that this method of treatment would be sufficient in the majority of cases of *P. falciparum* malaria in North Africa. In *P. vivax* infections, to prevent relapse, a prophylactic dose of 0·3 gm. should be taken weekly for several months after the treatment. There was no sign of drug intolerance in any case. *Norman White*

ASTRABADI, T. M. **Aralen New Antimalarial Remedy. Analysis of 60 Treated Cases.** *J. Faculty Med. Baghdad, Iraq.* 1949, v. 13, Nos. 4/5, 121–6.

The author opens with a general account of Aralen [chloroquine] and then discusses 60 cases of malaria treated by himself in Baghdad. There were 45 ***P. vivax*** and 15 ***P. falciparum*** infections.

The dosage schedule used consisted of 1 gm. as an initial dose, followed six hours later by 0·5 gm. On each of the following two days 0·5 gm. was given, making a total of 2·5 gm. The drug was given in the form of Aralen tablets of 0·25 gm. each.

Parasitaemia disappeared within an average of 48 hours, except for gametocytes of *P. falciparum*. Pyrexia disappeared in eight to 82 hours (average 23). In 42 patients, the temperature had subsided within 24 hours. Symptoms disappeared with the subsidence of fever. No toxic reactions were observed.

A case is quoted of a boy of ten with a *P. vivax* infection. In the first attack (when blood films were negative) he was given proguanil 0·1 gm. thrice daily for four days : the temperature fell, but rose again with daily remissions. *P. vivax* was then found in the blood and a " full adult course of aralen " was given. The temperature fell within 24 hours of the initial dose and remained normal for a fortnight : no parasites were found thereafter in two blood films taken at an interval of two days. *H. J. O'D. Burke-Gaffney*

CHAUDHURI, R. N. & CHAKRAVARTY, N. K. **Clinical Trials of CAM-AQI in Malaria.** *Indian J. Malariology.* 1948, Sept., v. 2, No. 3, 115–27, 6 charts.

Fifty-five patients suffering from malaria were treated with CAM-AQI. Twenty-seven received 0·1 gm. (base) twice daily for three days : 28 each received a single dose of 0·5 gm. (adult doses). There were 23 *P. falciparum*, 23 *P. vivax*, 6 mixed *P. falciparum* and *P. vivax*, and 3 *P. malariae* infections. The therapeutic response was prompt. Fever disappeared on the second day of treatment in 85 per cent. of cases treated by the first method and in 98 per cent. treated by the second method. Asexual parasites in the peripheral blood had disappeared on the third day in 83 per cent. of the patients : none was seen after the third day of treatment. The single-dose treatment terminated the clinical attack somewhat more quickly than the divided doses. *P. vivax* and *P. malariae* gametocytes disappeared within the five days following treatment. *P. falciparum* gametocytes were seen up to 26 days. Among 26 of the patients kept under observation from one to eight months there were eight parasitic and one clinical relapses : reinfection could not be excluded in some of these cases. The drug was well tolerated by all patients. It appeared to be equally effective in all three forms of infection. The authors consider that CAM-AQI would be suitable for the mass treatment of malaria patients in rural areas. *Norman White*

MOFFATT, J. S. **Contributions to the Chemistry of Synthetic Antimalarials. Part IX. Some Pyrimidine Derivatives.** *J. Chem. Soc.* 1950, June, 1603–6.

GELSI, R. & LACROIX, A. Un cas de paludisme chronique avec syndrome hémorragipare, traité par " l'hémochromatophénol " de Henry. [**A Case of Chronic Malaria with a Haemorrhagic Syndrome treated by Henry's " Haemochromatophenol ".**] *Bull. Acad. Nat. Méd.* 1950, v. 134, Nos. 19/20, 390–92.

REY VILA, F. Campaña de lucha antimosquito en la Isla Mayor del Guadalquivir (Sevilla). [**Antimosquito Campaign in the Isla Mayor del Guadalquivir.**] *Rev. Sanidad e Hig. Pública.* Madrid. 1949, Mar., v. 23, No. 3, 215–49, 15 figs. (11 on 4 pls.).

In the rice-growing district surrounded by the Guadalquivir and its branches [Isla Mayor del Guadalquivir] in the province of Seville, Spain, a large-scale field experiment with Gammexane was conducted against *Anopheles maculipennis atroparvus*. Malaria is endemic in the area which covers 4,000 hectares and houses 14,000–15,000 inhabitants.

The ceilings and walls of every building were treated with Gammexane at the rate of 0·5 gm. per square metre, twice during June to October 1947 and four times during March to October 1948. In addition five partial treatments were given at double the concentration to particular *Anopheles* shelters. Figures are given showing the incidence of malaria in 1944 and 1945 ; the number of cases for 1947 was only one-tenth of that for previous years, and in 1948 there was a further improvement.

It is suggested that in future years total treatment of the buildings should be given on 15th March, 1st June, 1st August and if necessary in late September. There should also be three partial treatments during the season for particular places and if the excellent results are continued, the author expects that malaria will cease to be a problem in the Isla Mayor del Guadalquivir.

H. S. Leeson

DAVIDSON, G. **A Field Study on 'Gammexane' and Malaria Control in the Belgian Congo. II. The Effect of the Spraying of Houses with 'Gammexane' on the Mosquito Population and on the Malaria Incidence in Children.** *Ann. Trop. Med. & Parasit.* 1950, Apr., v. 44, No. 1, 1–26, 5 figs.

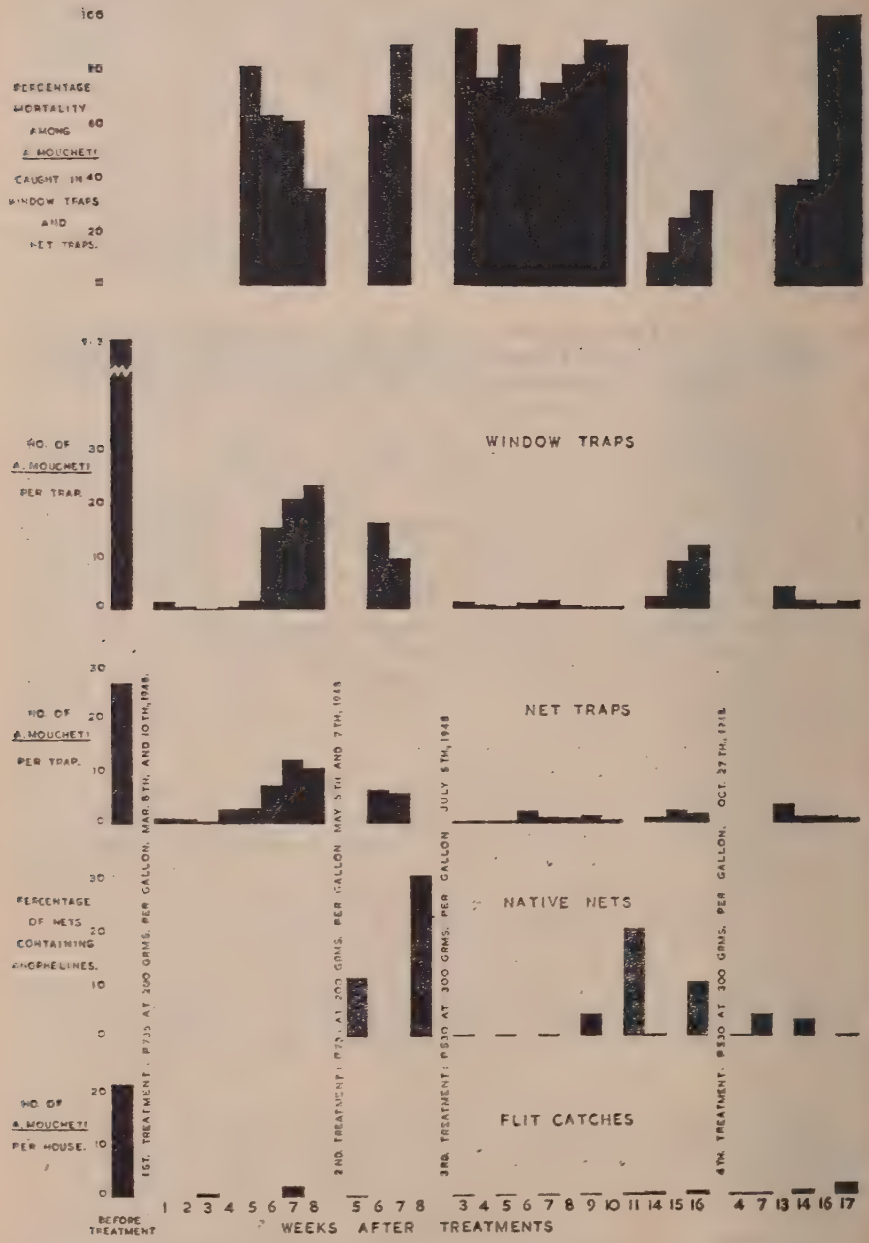
In the immediate vicinity of an oil palm plantation at Yaligimba (2°N. 23°E.) in the forest country of the Congo basin, certain more or less isolated villages, three to four kilometres from each other, were treated with Gammexane. These villages are described. The bionomics of the anophelines were the subject of an earlier paper [this *Bulletin*, 1950, v. 47, 597]. *Anopheles moucheti* was the common vector, together with *A. gambiae* under limited conditions. Observations were made in the villages and controls, before and after treatment with residual insecticide, to determine the effect on mosquito population in houses, mosquito infection rates, the general age of the mosquito population, the mortality rates among captured mosquitoes, mortality rates among mosquitoes exposed artificially to treated surfaces and the malaria incidence in children.

Effect on Mosquito Densities and Mortalities

A graphic analysis of numbers of mosquitoes (*A. moucheti*) found or caught weekly by " Flit " catches, native nets, net traps and window traps, is given for each village up to ten to 20 weeks after treatments. Mortalities are expressed as percentage of deaths among *A. moucheti* caught in net and window traps. The results for one village are shown in this abstract. Tables of monthly analysis of anophelines caught by each method are also given.

In summarizing his observations the author concluded that deposits of Gammexane at the rate of 10 mgm. of the gamma isomer per sq. foot of wall surface would appear to retain their toxicity against *A. moucheti* for three months. The density of *A. gambiae* was very low so that, apart from their absence after treatment, little evidence of effect was available. Culicines, predominantly *Taeniorhynchus* (*Mansonioides*) *africanus*, were little affected either in density or mortality by this dosage.

Although mosquitoes resting in houses during the day-time may remain negligible in numbers even up to four months after treatment—as in Madosso [see accompanying histogram] after the third and fourth treatments—significant numbers were entering, biting and leaving before that time. This would be expected if, after about three months, the insecticide had lost its toxicity to such an extent that those mosquitoes which spend only a part of one night in the treated houses leave before acquiring a lethal dose, but that those which remain after dawn and for the remainder of the following day still rest long enough to be killed. From a practical point of view the Flit-catching method alone does not accurately indicate the persistence-time



Analysis of the results of treatment of Madosso with Gammexane on the densities and mortalities of *A. moucheti*.

[Reproduced from the *Annals of Tropical Medicine and Parasitology*]

of the toxicity of the insecticide. For an accurate determination of that time, collections by window traps and net traps are essential, as well as observations on the mortalities among live mosquitoes caught by those methods.

Effect on Mosquito Infection Rates

The results of salivary gland examinations are summarized as follows :—

	No. of *A. moucheti*	No. positive	No. of *A. gambiae*	No. positive	No. of *A. paludis*	No. positive
Untreated Villages	3,927	15	651	25	63	0
Treated Villages	2,964	1	41	0	32	0

These results appear to indicate that in the treated villages mosquitoes were not living long enough to transmit malaria.

Effect on Age of the Mosquito Population

A study of the stomach and ovary conditions, the results of which are tabulated, indicates a reduction in the overall age of the mosquito population, even to preventing many from maturing and laying eggs ; *e.g.*, of 1,177 mosquitoes examined from treated villages, 1·53 per cent. showed evidence of previous egg-laying compared to 2·61 per cent. in untreated controls.

The Results of Artificial Application of A. moucheti *to Treated Surfaces*

By the use of wall application outfits the author was able to verify the lethal effects of treated surfaces from week to week. The results are tabulated and indicate a slight deterioration of lethal power in the 14 weeks of observation ; for the initial five weeks, 100 per cent. of mosquitoes exposed for half an hour were dead at six hours, whereas in the last two weeks 64 per cent. were dead at six hours, but none survived 24 hours.

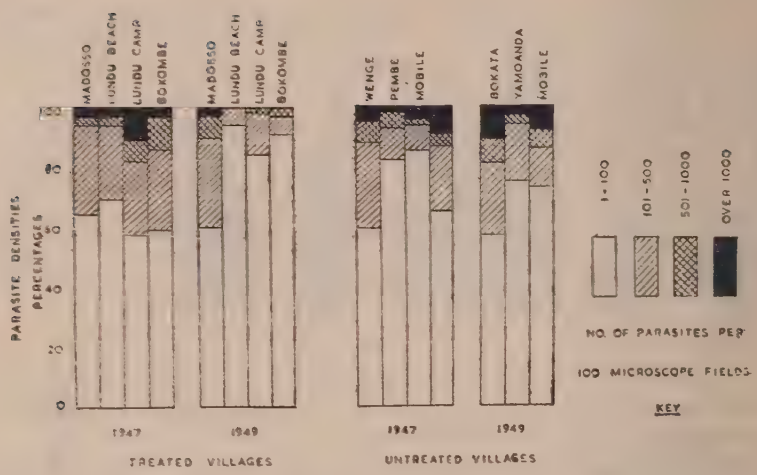
Effect on Malaria Incidence in Children

Parasite rates and intensities were determined just before residual insecticide was first applied and again about 12 months later in children, 70 per cent. of whom were below the age of five years.

A summary of the tabulated results is as follows :—

Villages	No. examined	Parasite rate %	Gametocyte rate %	No. of parasites per 100 microscope fields (percentage of all positive films)			
				1–100	101–500	501–1,000	Over 1,000
Before Treatment ...	534	84	19	66	23	6	5
After Treatment ...	250	84	21	81	15	3	1
Controls ...	214	92	24	67	19	6	8

There is little change in the parasite rates in the treated villages, but parasite counts showed a significant reduction in the intensity of the infections in all



Parasite intensities among children in villages treated with Gammexane and in control villages

[Reproduced from the *Annals of Tropical Medicine and Parasitology*]

except one village, as illustrated in the histogram. This is supported by a separate analysis of the results before and after in individual children.

The author observes that perhaps it is too early to expect better results at 12 months, as GIGLIOLI [this *Bulletin*, 1949, v. 46, 183] in British Guiana only observed significant results some two years after initial use of DDT. No significant difference was found between infant infection rates in treated and untreated villages. The great amount of movement of population which occurs throughout the area would probably tend to nullify the effect of residual insecticide on the malaria incidence in particular parts of the area.

[An abstract does not do justice to the detailed information contained in this paper, the result of a carefully planned field experiment.]

R. Ford Tredre

NAGENDRA, S. & NARAYANA MURPHY, K. S. **A Note on the Preliminary Trials with D.D.T. for the Control of Mosquito Breeding in Paddy Fields.** *Indian J. Malariology*. 1949, June–Sept., v. 3, Nos. 2/3, 165–90.

The experiments described were designed to assess the value of DDT in the control of mosquito breeding in inundated rice-fields. They were carried out near Bangalore. Measured plots were treated with either 2·5 or 1·25 per cent. emulsions of DDT, or with DDT in powdered form in concentrations of 5 or 2·5 per cent. As a control similar plots were treated with paris green or left untreated. The amount of DDT applied per acre was approximately two gallons of the emulsion or 24 oz. of the powder. The regular periodic larval collections were restricted to 15 dips: that this was insufficient is shown by the fact that the number of larvae captured in untreated plots were few. The results of the observations are set out in 22 pages of tables. They are not very informative. Many experiments were vitiated by the partial or complete drying up of the experimental plots before the observations were completed. If all these had been ignored there would have been little to report. The one conclusion that may be drawn perhaps is that the DDT emulsion was an

efficient larvicide. No damage to the rice crop resulted in any case. The larval collections included *Anopheles subpictus*, *A. annularis* and *Culex fatigans*.

Norman White

JASWANT SINGH & DALIP SINGH. **Control of Rural Malaria with D.D.T. Indoor Residual Spraying in Delhi Province during the Year 1948.** *Indian J. Malariology*. 1949, June–Sept., v. 3, Nos. 2/3, 129–44, 5 charts.

This is the second report on DDT residual spraying in the villages of Delhi Province [this *Bulletin*, 1949, v. 46, 17]. It describes the work carried out in 1948, a year in which rainfall and flood conditions resembled those of 1942, a year of epidemic malaria throughout the Indo-Gangetic Plains.

Spraying started on July 12 and ended on September 30 : the malaria transmission season is from July to November. One hundred and fifty-nine villages with spleen rates above 20 per cent. were sprayed twice : 89 other villages were sprayed only once. A DDT emulsion was used, 50 mgm. DDT per square foot. In addition antilarval measures were carried out within the three-mile belt surrounding the city and in 4 towns. The estimated annual cost *per caput* of the Delhi rural area was 5·1 annas. The results were gratifying. In neighbouring parts of India malaria was epidemic : in Delhi province the malaria incidence was lower than in any of the preceding four years. No infant infected with malaria was found in any of the sprayed villages.

Norman White

JASWANT SINGH & KARIAPA, C. B. **Malaria Control in Coorg.** *Indian J. Malariology*. 1949, June–Sept., v. 3, Nos. 2/3, 191–8, 1 map & 1 graph.

The small province of Coorg, of only 1,600 square miles, lies on the top of the Western Ghats in south India. The rainfall is excessive, vegetation profuse, and the climate temperate and very humid. Malaria was hyperendemic everywhere. If immigrants for work on coffee estates be excluded the population has decreased persistently for 50 years : deaths were generally in excess of births.

A special malaria unit started work in the beginning of 1947. Residual DDT spraying was started, at first with a kerosene solution and subsequently with a suspension. The province was divided into eight circles. The work in one of them, Mercara, is described in detail. It is typical of the work carried on in the other circles. Mercara, a small rural town, is the administrative capital of Coorg. *Anopheles fluviatilis* was the chief vector. *A. splendidus* was also commonly found. Other species collected were *A. maculatus*, *A. vagus*, *A. hyrcanus*, *A. karwari*, *A. jeyporiensis* and *A. philippinensis*.

In 1947 all houses were sprayed in March, May and October. In 1948 three rounds of spraying at intervals of eight weeks, commencing in January, were carried out : a final spraying was given in October, immediately after the monsoon. This procedure was also adopted in 1949. The results have been most satisfactory. Past records of spleen rates were uniformly high : 1919, 54·0 ; 1927, 55·4 ; 1946, 58·2 per cent. In January 1949 the spleen rate was only 10 per cent. The Mercara General Hospital records show a remarkable fall in malaria incidence. In the whole province 328 rural towns and villages, containing 22,744 dwellings and 11,121 out-houses, with a combined population of 123,401, were treated in the manner described above. Every coffee estate management adopted regular DDT spraying under guidance. An instance is given which illustrates the remarkable improvement in the health of agricultural

workers. The *per capita* cost of the measures was 10·8 annas per annum. No malaria infection was found in any infant born after the commencement of DDT spraying. *Norman White*

PERU: PUBLICACIONES DE LA DIRECCIÓN GENERAL DE SALUD PUBLICA. DEPARTAMENTO DE MALARIA. Lima, 1949. Oct., 19 pp., 5 graphs. La malaria en el valle de Cañete. Desarrollo de la campaña antimalárica en el lapso 1944–1948. **Malaria in the Canete Valley: Progress of the Antimalaria Campaign during 1944–1948.**

Malaria was formerly endemic in the Canete Valley. This was revealed by a survey carried out in 1936 under the direction of Professor Carlos E. PAZ SOLDAN, and confirmed in 1943 when a mean spleen index of 22 per cent. was reported. Four circumstances determined the prosecution of an energetic antimalaria campaign: the economic prosperity of the valley; its relatively dense population; malaria endemicity; and the possibility of obtaining economic collaboration with agriculturists, industrialists and others interested in the prosperity of the region. The valley has 25,000 hectares of cultivated land and there is a large seasonal migration of native agricultural workers, many of whom come from regions which are free from malaria. The malaria vector is *Anopheles pseudopunctipennis*.

From 1944–47 time-honoured methods of malaria control were employed, chemical larvicides, drainage, filling, attention to canals and water courses and the like. All malaria patients were adequately treated. In 1947 house spraying with DDT was started. A series of tables and graphs show the remarkable results achieved. Malaria has been almost eliminated from the valley. Of 3,123 children whose blood was examined in October–December 1948, none was found harbouring parasites. None of 43 children between the ages of 2 and 5 had enlarged spleen. The splenic indices of 1,213 children of from 5 to 9 years, and of 1,867 from 10 to 14 years were 0·16 and 0·10 per cent., respectively. Malaria patients treated in the special dispensary, in whom the diagnosis was confirmed microscopically, numbered 3,750 in 1944: in 1947 there were 22 and in 1948 only 2. *Norman White*

HILL, R. B. **Mosquito Control Activities in the Caribbean Area.** Presented at the 20th Annual Meeting of the Florida Anti-Mosquito Association, Mount Dora, Florida, Apr. 3–6, 1949. 10 pp.

In this summary the author takes the territories in the Caribbean Area one by one and describes the mosquito control activities taking place in each.

A pilot experiment against anophelines with residual DDT spraying was done in several villages in Panama. In one year the incidence of malaria was reduced to levels hitherto unknown. In another year's time the disease had almost disappeared. All over the Caribbean area, Health Departments thereafter extended their residual spraying programmes according to their means and available assistance and the tendency now is for countries to combine their *Anopheles*, *Aëdes aegypti* and other mosquito services into an antimosquito service with greatly increased efficiency of operation.

Some of the outstanding achievements reported are as follows. Brazil has eliminated *Aëdes aegypti* from all but a small area in the north-east; Bolivia has been free of this mosquito for some years; British Guiana is 95 per cent. free and Peru, Chile, Venezuela and Surinam are working towards eradication.

In Venezuela malaria has declined so remarkably that the malaria hospital at Maracay has had to be closed for lack of patients and whereas the spleen

rates in five selected towns used to vary between 75 and 100 per cent. they were down to 3 to 15 per cent. in 1949. Malaria in Trinidad due to *Anopheles bellator*, which breeds in the bromeliads on the immortelle trees which shade the cacaos, has practically disappeared in the 2,000 acres where the bromeliads have been destroyed by the copper sulphate treatment, and in five years they have not reappeared. Coastal malaria caused by *A. aquasalis* is being reduced by residual DDT spraying of 30,000 houses twice a year. *Aëdes aegypti* and *Anopheles darlingi* have both been eliminated from a large part of British Guiana. Residual spraying has been discontinued in Georgetown which is protected by a barrier of DDT-treated buildings. The stirrup pump, as used in Britain for fire-fighting during the war, has replaced the usual spraying equipment.

The author concludes with the warning that the residual insecticides are not the complete answer to the mosquito control problems ; they are at best but palliatives which must be regarded as temporary but powerful additions to other measures, especially those permanent ones which reduce breeding places. *H. S. Leeson*

HUGHES, Hettie B. & SCHMIDT, L. H. **Metabolism of various 8-Aminoquinolines in Rhesus Monkey.** *Proc. Soc. Exper. Biol. & Med.* 1950, Apr., v. 73, No. 4, 581–5.

During routine tests in monkeys it was found that CN 1100 [2-methoxy-8-(3 aminopropylamino)-quinoline] had a very much lower oral or parenteral toxicity than about 200 other 8-aminoquinolines which have been so widely investigated as antimalarials. The substance was estimated in plasma by the well-known method of BRODIE *et al.* [this *Bulletin* 1947, v. 44, 793] in which extraction by ethylene dichloride followed by diazotization to give a coloured derivative is used. It was found that much higher results were obtained if the extraction were omitted and the diazotized coupling reagent, in this case sulphanilic acid, was added directly to diluted plasma. Part of the colour production was due to alkali-soluble but ethylene dichloride-insoluble metabolic product or products of the drug. Similar experiments were made with the 6-methoxy-8-aminoquinolines pamaquin (plasmoquine), isopentaquine, primaquine, pentaquine and the two 2-methoxy-8-aminoquinolines SN 13,058 and CN 1100. All six substances, after oral or intramuscular administration, gave rise to an alkali-soluble, ethylene-dichloride-insoluble metabolic fraction, that from CN 1100 being relatively the largest. It was noted that the peak concentration of the ethylene dichloride-soluble fraction in plasma was reached within ½-hour after intramuscular injection, whereas the ethylene dichloride-insoluble fraction did not reach a peak value till approximately two hours after administration, and this peak was in some cases apparently very much higher than that of the unchanged drug (soluble in ethylene dichloride). Experiment indicated that these findings were due to a more intense production of colour by the metabolic products of the parent substance. Large quantities of the metabolic products with characters similar to the above were also found in the urine of monkeys, and could be extracted with butanol. The interest of these investigations lies in the acidic character of the metabolic products formed by some well-known antimalarials, which appears to have escaped attention, and suggests that further metabolic studies are desirable. *J. D. Fulton*

COVALEDA ORTEGA, J. & GÁLLEGO BERENGUER, J. Hemoproteus aviares. [*Haemoproteus* **in Birds.**] *Rev. Ibérica de Parasit.* 1950, Apr., v. 10, No. 2, 141–85, 6 pls. [51 refs.]

TRYPANOSOMIASIS

FERREIRA, F. S. da C. Relatório do Chefe da Missão de Estudo e Combate da Doenca do Sono na Guiné referente ao ano de 1948. [**Report of the Mission for Studying and Combating Sleeping Sickness in Portuguese Guinea.**] *Anais Inst. Med. Trop.* Lisbon. 1949, Dec., v. 6, 553–603, 6 charts & 2 coloured maps.

This is a report for 1948 of the activities of the Mission, its third year of action, with references here and there to the two preceding years. The number of persons examined during 1948 was nearly 9,000 less than in 1947, but 56,480 more than in 1946 and the number of cases of sleeping sickness discovered has risen markedly—404, 782 and 1,272 in the three years respectively. Of these 1,272 the sex incidence was nearly equal, 666 males and 606 females ; 137 were children, 436 were adolescents, 692 were adults and 7 were aged [the ages of each of these groups are left undefined]. Those dealing with the discovery and treatment of patients are divided into 5 sectors with main base installations and 10 treatment posts, one sector having 4, another 3 and the rest one such post each. The numbers examined by each of these sectors and the number of cases of trypanosomiasis are given for each half-year and the work of the different laboratories is mentioned and the results of capture and study of Glossinae. Of 1,935 flies caught (1,279 males and 656 females), 544 were dissected and 15 (9 males and 6 females) were found infected, *i.e.*, 15 out of 544 (2·7 per cent.).

Incidental activities, as they might be called, that is observations on diseases other than trypanosomiasis, included inquiries into ankylostomiasis [no figures are given], leprosy (104 patients were discovered in the first half of the year and 219 in the second), 323 cases, almost the same as in the previous year, 327. In view of these by-studies it is proposed to convert the Sleeping Sickness Mission into a mobile General Health Service. A list of 14 articles or reports published during the year, or in the Press, is given.

Two special investigations have been pursued. First, the biology of *T. brucei* and *T. gambiense* in laboratory animals and their pathogeny ; second, the biology of the Glossinae with a view to deciding the best method of agronomic prophylaxis. There are two clear maps coloured to show, one the distribution of *G. palpalis*, *G. longipalpis*, *G. submorsitans* and *G. fusca* ; the other indicating the prevalence of the disease in different parts of the country. Prophylactic measures include systematized capture of tsetse in permanent foci where they are numerous ; agronomic as by deforestation and cutting down of bush, especially at water-sites where people congregate ; intensification of vegetable cultivation and improvement of house construction.

Mention has been made of the ancillary activities of the Mission and the proposal is now put forward to regard it as a Health Unit with wider scope, to deal with ankylostomiasis, dracontiasis, filariases and leprosy. [See also this *Bulletin*, 1949, v. 46, 1013.] *H. Harold Scott*

CHORLEY, J. K. **Tsetse Fly Operations in Southern Rhodesia. Short Survey of the Situation in the Year ended December, 1946.** *Rhod. Agric. J.* 1947, v. 44, No. 5, 520–31, 1 folding map ; also as *Bull. Minist. Agric.* [*S. Rhod.*] 1947, No. 1419, 13 pp., 1 folding map. [Summary taken from *Rev. Applied Entom.* Ser. B. 1950, June, v. 38, Pt. 6, 105–6.]

During 1946, the incidence of trypanosomiasis of cattle on farms in the Chipinga area of the Eastern Border of Southern Rhodesia continued the progressive decline that has been seen in recent years with the exception of

1945. Flies caught in Portuguese East Africa on or near the border comprised 39 examples of *Glossina pallidipes*, Aust., one of *G. brevipalpis*, Newst., and 17 of *G. morsitans*, Westw., and two of *G. morsitans* were taken on the Rhodesian side. The fact that no examples of *G. brevipalpis* or *G. pallidipes* were caught inside the border is attributed to the cutting out of some heavily forested ravines. A number of cases of trypanosomiasis of stock occurred in two mountain farms in the Melsetter district situated above the normal limit of *Glossina* infestation but connected by forest leaders with low-lying valleys on the border of Portuguese East Africa, known to be infested with *G. pallidipes* and *G. brevipalpis*. Further south, administrative difficulties and shortage of water and grazing prevented the creation of the cattle-free zone along the border authorised in the previous year and the position with regard to *G. morsitans* continued to deteriorate. A very heavy infestation was found on the Ndanga River, in Portuguese East Africa, within one mile of the border, and 42 flies were taken inside Southern Rhodesia on the same river in three days. South of the Sabi River, the edge of the fly belt in Portuguese East Africa appears to have remained stationary about 20 miles from the border. Seven cases of trypanosomiasis were diagnosed from cattle near the Portuguese border just east of Umtali township. There was evidence of a small but well-established focus of *G. morsitans* near the border of Umtali and Portuguese East Africa in August, but a careful survey in November and December failed to produce any more examples.

In the Urungwe district, in the Zambesi Valley, 13 cases of sleeping sickness were diagnosed in natives, the highest number for many years. In all the northern areas covered by controlled operations for the elimination of game, densities of *G. morsitans* were further reduced. Only a few isolated foci in three areas remain to be dealt with to complete the clearing of some 10,000 sq. miles. A threat that *G. morsitans* will enter the Mtoko area from Portuguese East Africa has increased, and though it has not been seen within the area there is much more trypanosomiasis of stock. A brief account is given of the situation in individual districts and of incidental control measures taken, particular attention being devoted to the history of infestation by *G. morsitans* in the Hartley area, from which the fly has almost been exterminated.

Ferreira, F. S. de C. & de Almeida, C. L. O valor da punção esternal no diagnóstico da tripanosomiáse humana. [**The Value of Sternal Puncture in the Diagnosis of Trypanosomiasis.**] *Anais Inst. Med. Trop.* Lisbon, 1949, Dec., v. 6, 65–70, 2 figs. on 1 pl. English summary.

Trypanosomes were found in the sternal marrow of 13 out of 42 persons with sleeping sickness in Portuguese Guinea in whom no trypanosomes could be seen in the blood (thick films and triple centrifugation), lymphatic glands or cerebrospinal fluid ; the proportion was highest in children (7 out of 14). The authors conclude that sternal puncture is useful in suspected cases of sleeping sickness when other methods of examination have failed to show the presence of trypanosomes. The sternum was punctured with a trocar (illustrated) at the level of the second intercostal space under local anaesthesia with novocain.

J. F. Corson

Gasq, M. Glycémie et glycorachie comparées chez le noir sain et trypanosome. [**Glucose Content of the Blood and Cerebrospinal Fluid in Normal and Trypanosome-Infected Africans.**] *Méd. Trop.* Marseilles. 1950, Jan.–Feb., v. 10, No. 1, 105–11.

Most of the information, and the main conclusions of this paper, have already been published [Gasq, this *Bulletin*, 1950, v. 47, 447]. *E. M. Lourie*

DAVEY, D. G. **Experiments with "Antrycide" in the Sudan and East Africa.** *Trans. Roy. Soc. Trop. Med. & Hyg.* 1950, May, v. 43, No. 6, 583–616.

The author records field investigations on Antrycide [see CURD and DAVEY, this *Bulletin*, 1949, v. 46, 338; 1950, v. 47, 827] carried out between January 1948 and April 1949.

Preliminary tests were done in the Sudan, and the work was then extended to Uganda and Kenya. In the Sudan shorthorn Zebu cattle were used; in Uganda, Ankole cattle with some Zebu; and in Kenya a variety of mixed European breeds and also Zebu.

Antrycide chloride is absorbed slowly and poorly, but the methylsulphate rapidly and fairly completely. Consequently, when given subcutaneously or intramuscularly, a suspension of the chloride is less toxic than an equivalent solution of the methylsulphate, and its delayed absorption accounts for its prophylactic property. For curative effect in large animals the methylsulphate should be superior to the chloride.

The criterion adopted for cure was the absence of trypanosomes from thick blood films examined almost daily for 112 days. Against 3 strains of *T. congolense* in cattle the curative dose of the methylsulphate subcutaneously was about 1 mgm. per kgm., and against a fourth it was about 2 mgm. per kgm. Against two strains of *T. vivax* the curative dose was somewhere between 1 and 5 mgm. per kgm. "The latter dose (5 mg. per kg.) has been suggested as the field dose because it errs on the generous side in the treatment of *T. congolense*, and has cured those strains of *T. vivax* which have been tested." The dose has been used by J. T. R. EVANS in the Sudan in about 200,000 cattle "with almost entirely satisfactory results, disquiet only arising when calves were being treated."

In prophylactic experiments, protection was tested usually by syringe-infection but sometimes by tsetse bite. The methylsulphate in a dose of 5 mgm. per kgm. failed to protect against *T. congolense* for 12 weeks, but the same dose of chloride protected in all cases for this period of time, and usually for as long as 24 weeks, negative films for at least 84 days being regarded as evidence of protection.

Two field experiments were conducted in tsetse areas, one in Nsongezi, Uganda, and the other in Kiboko, Kenya. In Nsongezi 10 animals received 2 gm. of the methylsulphate and 10 received 1·5 gm. of the chloride. Only one of the treated animals developed *T. congolense* infection, in the 20th week, but *T. vivax* infections began to appear in the 11th week after the methylsulphate and in the 14th week after the chloride. In Kiboko 10 animals received 3 gm. chloride, and 34 received varying mixtures of chloride and methylsulphate. Two animals treated by methylsulphate alone, and 6 treated by mixtures, developed *T. congolense* at various times after the 14th week. After the optimum mixture of 1·5 gm. methylsulphate plus 2 gm. chloride *T. congolense* was first seen in the 21st week. *T. vivax* infections were more frequent, beginning at the 9th week after the methylsulphate and the 13th week after a mixture. Unprotected control animals in both areas died of trypanosomiasis within 12 weeks. Re-treatments, under circumstances such as those of the field experiments described, are recommended after 8 weeks, or, if *T. vivax* be regarded as of less importance, after 12 weeks.

Evidence of Antrycide-resistance was sought in the susceptibility to treatment of (1) relapsed infections after an ineffective first course, (2i) break-through strains which appeared in the prophylactic experiments, (2ii) break-through strains of *T. vivax* obtained by repeatedly applying infected tsetse flies to treated cattle, and (2iii) break-through strains of *T. congolense* obtained in the Kiboko field experiment. For (2iii) rats or mice were subinoculated and were

then examined in Manchester. It was in series 1, and more particularly in (2iii), that the main evidence of resistance emerged.

With regard to toxicity, this is negligible for the chloride when given subcutaneously, intramuscularly or orally, and only local swellings of no consequence occur. As for the methylsulphate, it is recommended that the subcutaneous dose should not exceed 12 mgm. per kgm., and animals should be kept as quiet as possible for 12 hours after treatment. It is, however, wisest to adhere closely to the recommended field dose of 5 mgm. per kgm. Deaths have occurred after as little as 2·5 mgm. per kgm. of the methylsulphate in cattle that have been mishandled and chased immediately after treatment. *E. M. Lourie*

SCHOENAERS, F. Premiers résultats d'un essai de chimiothérapie des trypanosomiases bovines à *Trypanosoma congolense* et *Trypanosoma vivax* par l'Antrycide. [**Antrycide in the Treatment of** *T. congolense* **and** *T. vivax* **Infections in Bovines.**] *Ann. Soc. Belge de Méd. Trop.* 1950, Mar. 31, v. 30, No. 1, 65–8.

Twenty random infections (13 of *Trypanosoma congolense* and 7 of *T. vivax*) in native herds at Kisenyi, Ruanda, were treated with Antrycide methylsulphate. The drug was administered subcutaneously in a dose slightly less than 5 mgm. per kgm. *T. congolense* disappeared in 6 to 8 hours. In one of the *T. vivax* infections a few trypanosomes were still present in 24 hours, but were gone by the next day. Local swellings after injection reached the size of a fist and usually resolved in 5 to 7 weeks.

Drs. WÉRY and THIENPONDT reported a relapse of *T. vivax* in a bull calf 2 months after treatment (dose not stated). It responded to re-treatment without evidence of drug-resistance. *E. M. Lourie*

DEOM, J. Chimioprophylaxie des trypanosomiases bovines à *T. congolense* et *T. vivax* par le Phénanthridinium S.1553. [**Dimidium Bromide for Chemoprophylaxis against Bovine** *T. congolense* **and** *T. vivax* **Infections.**] *Ann. Soc. Belge de Méd. Trop.* 1950, Mar. 31, v. 30, No. 1, 25–9.

Solutions of dimidium bromide, ready for use in a concentration of 1 per cent., can be safely stored in brown well-stoppered bottles, and have been successfully used after being kept in this way for 6 to 12 months.

In tests for prophylactic action 25 cattle were treated intramuscularly by 1 mgm. per kgm., and heavy suspensions of *T. congolense* or *T. vivax* were then injected intravenously, once into each animal, 5 minutes to 28 days after treatment. All unprotected controls became infected, but among the treated animals trypanosomes (*T. congolense*) were found in only 3 cases, where the intervals between treatment and the test-inoculation were 7 days, 9 days and 14 days, respectively. The longest observation-period seems to have been only about 2 months. *E. M. Lourie*

PARKER, J. P., EWING, P. L. & EMERSON, G. A. **Lack of Antagonism of Malononitrile and Desoxyribonucleic Acid to Trypanosomiasis, Alloxan Diabetes and Lethal Effects of X-Irradiation.** *Texas Reports on Biol. & Med.* 1950, v. 8, No. 2, 257–61. [10 refs.]

"Neither malononitrile nor desoxyribonucleic acid, in massive repeated doses, has appreciable effects on experimental trypanosomiasis, alloxan diabetes, or lethal effects of X-irradiation in mice."

RENJIFO-SALCEDO, S. & OSORNO-MESA, E. *Dasypus novemcinctus*, procedente de Ocoa, Villavicencio, Meta, naturalmente infectado con *Trypanosoma cruzi* Chagas. [*D. novemcinctus* **Naturally Infected with** *T. cruzi* **in Ocoa, Villavicencio, and Meta (Colombia).**] *Rev. Acad. Colombiana de Ciencias Exactas, Fisicas y Naturales.* 1950, May, v. 7, No. 28, 548, 2 pls.

FEVERS OF THE TYPHUS GROUP

BOVARNICK, Marianna R. & MILLER, Judith C. **Oxidation and Transamination of Glutamate by Typhus Rickettsiae.** *J. Biol. Chem.* 1950, June, v. 184, No. 2, 661–76. [22 refs.]

ROBIN, L. A. La réaction de Weil-Félix chez le chien domestique. [**The Weil-Felix Reaction in Domestic Dogs.**] *Rev. Méd. Française d'Extréme-Orient.* 1942, Oct.–Nov.–Dec., v. 20, Nos. 8, 9 & 10, 1017–19.

HAWKSLEY, J. C. & STOKES, E. Joan. **A Case of Brill's Disease in London.** *Lancet.* 1950, July 15, 97–9, 1 chart. [19 refs.]

This is the first case of the Brill type of typhus fever that has been diagnosed in London.

The patient, aged 49 years, was born in Poland where she suffered from a severe attack of typhus fever in 1915. The illness now described occurred in September, 1948, and although no rash was detected Brill's disease was suspected. On the 12th day of the illness the Weil-Felix reaction was positive at a titre of 1–200 with *Proteus OX19* and *OX2*. The *OXK* titre was 1–80. From the 18th day onwards several check tests were carried out under the supervision of Dr. A. Felix at the Public Health Laboratory, Colindale, London, and from the 27th day onwards samples of the serum were tested by Dr. R. L. Gauld at the Army Medical Centre, Washington, U.S.A. Some examples of the results are given below.

Day of disease	Weil-Felix Test Hospital Lab.			Colindale			Complement Fixation Washington		Rickettsia Agglutination Washington	
	OX19	*OX2*	*OXK*	*OX19*	*OX2*	*OXK*	Epidemic	Murine	Epidemic	Murine
18 ...	700	160	—	800	25	50	—	—	—	—
27 ...	200	40	40	800	25	50	640	40	0	0
38 ...	120	—	—	400	25	50	1,280	160	640	0
59 ...	40	20	20	200	25	50	1,280	160	320	40
191 ...	40	20	20	100	25	50	160	20	80	40

Dr. Gauld was surprised at the delayed occurrence of the rickettsia-agglutination reaction, which in his experience usually becomes positive earlier than the complement-fixation reaction.

A comment on the results, contributed by Dr. Felix, is referred to below.

John W. D. Megaw

FELIX, A. **Note on a Case of Brill's Disease in London.** *Lancet.* 1950, July 15, 99–100. [15 refs.]

In a valuable discussion of the laboratory findings referred to in the above abstract the author mentions that the diagnosis was made because the attending physician had considerable experience of typhus fever in the Middle East.

The need for standardization of the Weil-Felix technique is again stressed by the author who now states that his proposal for the adoption of international serum standards has been accepted by the Committee on Biological Standardization of the World Health Organization.

Reference is made to the frequent reports of failure of the Weil-Felix test in cases of Brill's disease and the suggestion is made that unsatisfactory technical methods may be responsible. In the present study the tests carried out in two laboratories in London sometimes showed a four-fold difference in the titres recorded for the same sera.

Mention is made of the possibility that cases of Brill's disease may play a part in disseminating typhus fever; the experiments of MURRAY *et al.* show that lice readily become infected by feeding on patients in the early stages of the disease [see this *Bulletin*, 1950, v. 47, 729].

The author knows of only one case in which Brill's disease has been recognized outside the coastal towns of the U.S.A. ; this is the case reported by MOOSER & LÖFFLER in Switzerland [see this *Bulletin*, 1946, v. 43, 543], but quite recently three cases reported by WORMS from Paris were justifiably regarded as being of the Brill type [see this *Bulletin*, 1950, v. 47, 833]. Brill's disease, now known to be a recrudescence of a persisting typhus infection, is likely to be detected with increasing frequency among persons who have had attacks of louse-borne typhus. *John W. D. Megaw*

DONZELOT, E., KAUFMANN, H. & VERNANT, P. L'endocardite infectieuse subaiguë primitive; ses rapports avec le typhus exanthématique. [**Primary Subacute Infective Endocarditis: its Relationship to Exanthematic Typhus.**] *Bull. et Mém. Soc. Méd. Hôpit. de Paris.* 1950, Nos. 9/10, 379–86. [29 refs.]

The author gives further details of the 23 cases of endocarditis already reported as late complications of louse-borne typhus [see this *Bulletin*, 1950, v. 47, 613].

The special features were : (1) complete absence of evidence of previous cardiac lesions ; (2) the special involvement of the aorta and myocardium ; (3) negative blood cultures ; (4) an increase in the gamma globulin ; (5) resistance to penicillin treatment ; and (6), in the most recent cases, evidence of benefit from aureomycin.

Only two of the first 18 patients survived and these still suffered from severe cardiac sequelae, whereas two of three recent patients showed rapid improvement after aureomycin treatment.

The author suggests three hypotheses : (1) a streptococcus infection associated with endothelial damage caused by an attack of typhus fever ; (2) a rickettsial endocarditis ; and (3) a combination of the above two conditions. *John W. D. Megaw*

WORMS, R., PÉQUIGNOT, H. & HELD, J. P. Endocardite subaiguë d'apparence primitive et typhus exanthématique. [**Subacute—apparently Primary—Endocarditis and Exanthematic Typhus.**] *Bull. et Mém. Soc. Méd. Hôpit. de Paris.* 1950, Nos. 9/10, 412–14.

The authors describe a case of malignant endocarditis which occurred in a young man who had suffered from a confirmed attack of typhus fever five

years previously, and had since been apparently in perfect health. The recent illness responded well to penicillin treatment. The Giroud serum-protection test for typhus fever was positive.

The authors admit that the evidence submitted by DONZELOT *et al.* [above] is impressive but they find it impossible to dogmatize with regard to the nature of the relationship between the endocarditis and typhus fever. They comment specially on the complete absence of evidence of recrudescence of rickettsial activity and hope that further investigation will throw light on the problem. They agree that the question of a previous attack of typhus fever must be taken into account in every case of apparently primary endocarditis.

[The absence of serological evidence of a flare-up of rickettsial activity may not necessarily exclude a local activity in the affected tissues. In view of the pathology of the typhus group of fevers it is surprising that there have been so few reports of permanent damage to the cardiovascular system.]

John W. D. Megaw

RUIZ SANCHEZ, F. El tratamiento del tifo exantematico con acido para-aminobenzoico, aureomicina y cloromicetina. Estudio comparativo. [**A Comparative Study of the Effects of Treatment of Exanthematic Typhus Fever with Para-aminobenzoic Acid, Aureomycin and Chloromycetin.**] *Medicina.* Mexico. 1950, Apr. 25, v. 30, No. 602, 165–76, 12 figs.

Louse-borne typhus fever is endemic in Guadalajara, Mexico, where it occurs in a mild form with a fatality rate of 2 to 5 per cent.

The 24 cases treated with para-aminobenzoic acid ran the usual course apart from some relief to the headache and pains. The author states that large doses of more than 20·0 gm. daily were badly tolerated.

Aureomycin was given to 42 patients in divided doses by the mouth ; the daily dosage was 50/75 mgm. per kilo. of body weight, and treatment for 36 hours was usually enough. In 32 cases the temperature fell to normal less than 36 hours after the first dose. The total duration of the fever averaged nine days as compared with 14 days in untreated cases. Nausea and vomiting often occurred but did not necessitate interruption of the treatment.

Chloromycetin was given to 14 patients orally, usually at the rate of 50 mgm. per kilo. of body weight, but in four cases the dosage was 75 mgm. per kilo. Of the ten patients who received the smaller doses, four were still febrile 72 hours after the first dose, which in each case was given on the sixth day of the illness. Two of these four patients were treated for 36 hours, the other two for 60 hours.

An interesting feature of the trial was that six of the 14 patients had a relapse 48 to 78 hours after the temperature had fallen to normal, but all responded well to a further course of treatment. Only one of the patients showed signs of intolerance.

The author regards aureomycin as the drug of choice but considers chloromycetin to be of great value, especially for patients who are intolerant of aureomycin.

John W. D. Megaw

ROY, I. B. **Typhus in Mylliem State Area, Shillong.** *Indian Med. Gaz.* 1950, Mar., v. 85, No. 3, 99–101.

The author found that fevers of the typhus group were relatively common in the hill tracts round Shillong, Assam. Among 61 cases there were seven deaths. The Weil-Felix test was carried out in 16 cases, but in six of these only one test, on or before the seventh day, was carried out. Eight of the ten patients tested after the ninth day reacted with *Proteus OX19* at titres of

1–125 to 1–300 ; the other two gave reactions of the *OX2* type at titres of 1–125 and 1–150 respectively. In an editorial footnote it is suggested that two of the cases look like tick-borne typhus. *John W. D. Megaw*

ORTIZ MARIOTTE, C., VARELA, G., ROCH, E. & GONZALEZ ROBLES, F. Rickettsiasis en Uruapan. Informe preliminar. [**A Rickettsial Disease, Murine Typhus, in Uruapan.**] *Medicina*. Mexico. 1950, May 25, v. 30, No. 604, 205–12, 4 graphs, 1 fig. & 1 plan.

The authors have found that murine typhus is endemic in Uruapan, a town with a population of 24,272 at an elevation of about 5,000 feet in the State of Michoacán, Mexico.

In all the 53 cases examined the Weil-Felix reaction (*Proteus OX19*) was positive, but among the 23 cases tested between the 6th and 12th day by the complement-fixation test only three were positive with murine antigen and two with epidemic antigen. Later fixation tests were carried out on ten patients and nine of these gave a reaction of the murine type.

Four out of 17 rats examined gave positive fixation reactions of the murine type. A guineapig inoculated with a suspension of fleas from the rats reacted in a manner consistent with murine infection, and mention is made of the isolation of a murine strain from a patient.

The epidemiological conditions are described ; these were in keeping with the diagnosis of murine typhus. *John W. D. Megaw*

ROBBINS, Mary L., BOURKE, Anne R. & SMITH, P. K. **The Effect of certain Chemicals on *Rickettsia typhi* Infections in Chick Embryos.** *J. Immunology*. 1950, May, v. 64, No. 5, 431–46. [50 refs.]

This important paper contains a concise description of an extensive original study of the rickettsiostatic action of 315 chemicals on *Rickettsia mooseri*, and a brief, but comprehensive, review of the whole subject of rickettsiostatic drugs.

The name *R. typhi* is used instead of the more familiar *R. mooseri*, which, however, seems likely to survive the challenge to its validity.

The method employed in the study was the usual one of injecting tolerated quantities of the drugs into the yolk sacs of embryo chicks on the seventh day of incubation and immediately inoculating the sacs with a standard dose of virulent rickettsiae. The efficacy of the drugs was estimated by observing the survival period of the embryos as compared with that of control embryos inoculated in the same way but not treated with the drugs. Nearly all the tests were carried out on two occasions, 15 or more eggs being tested against corresponding numbers of controls.

Only 25 of all the chemicals tested caused a prolongation of the average time of survival by one day or more, and 13 of these were substances already known to have a rickettsiostatic effect, so that 12 out of about 300 chemicals tested for the first time were regarded as being effective.

From the tables it appears that the following chemicals caused a prolongation of the survival period by 2·5 days or longer : (*a*) of the newly tested chemicals just two reached this standard ; one was a drug very closely related to paludrine [proguanil], 1-(p-chlorophenyl) biguanidine HCl ; the other was dodecamadine HCl ; (*b*) among previously tested chemicals the following gave the prolongation periods shown in brackets : aureomycin (5·13) ; streptomycin (4·6) ; chloramphenicol (6·84) ; penicillin G (2·46) ; penicillin dihydro F (5·28) ; penicillin K (3·74) ; and penicillin X (5·46).

Para-aminobenzoic acid (1·20), salicylic acid (1·56), methylene blue (2·01), toluidine blue (2·01), malachite green (1·67), and acriflavine (2·08) were the other drugs which had previously been tested.

The results obtained with the different penicillin fractions differed from those reported by GREIFF and PINKERTON who, using a somewhat different method of comparison, found penicillin K, F, and dihydro F fractions less effective than penicillin G, but their finding with regard to the superior effect of penicillin X agreed with that of the present study [see this *Bulletin*, 1949, v. 46, 246].

Apart from the fact that several substances related to para-aminobenzoic acid were effective there was little correlation between rickettsiostasis and chemical structure : for example paludrine was completely ineffective despite its close relationship to 1-(p-chlorophenyl) biguanidine HCl.

Cysteine was found to inhibit the rickettsiostatic action of penicillin G.

John W. D. Megaw

WOOLF, C. R. **Murine Typhus : its Pathology.** *South African Med. J.* 1950, June 24, v. 24, No. 25, 481–4. [16 refs.]

The author describes in detail the post-mortem findings in a case of murine typhus. The patient, aged 68 years, died of a massive pulmonary embolism which occurred about the 27th day of the illness.

The rickettsia-agglutination and complement-fixation reactions were at significantly higher titres for murine than for epidemic typhus.

The most striking lesion was acute diffuse myocarditis with infiltration by mononuclear leucocytes, plasma cells and lymphocytes.

There were small foci of myocardial degeneration. No typhus nodes were found in the brain and there was no significant swelling of the cells of the capillaries or small blood vessels ; the author tentatively suggests that the absence of these two features may differentiate murine typhus from the louse-borne disease, but he rightly states that the evidence available is too scanty to justify the expression of a definite opinion on the subject.

John W. D. Megaw

MARTIN, R., MONTEL, L. R. & VARGUES, R. Typhus de laboratoire et chloromycétine à propos d'une auto-observation. [**Laboratory Typhus and Chloromycetin. A Personal Experience.**] *Bull. Soc. Path. Exot.* 1950, v. 43, Nos. 5/6, 259–65, 1 chart.

This is a vivid description of an attack of murine typhus, which in the early stage was so severe as to threaten the life of the patient, a medical man aged 71 years, who had been inoculated against typhus in 1945 and again in 1946. He had been working in the same room as a colleague who was preparing a large number of smears of *Rickettsia mooseri* for class purposes ; on the following day he had a severe attack of catarrh of the eyes, nose, and throat which subsided in three days. Six days after exposure to infection his temperature rose rapidly and remained high. On the fourth day of the fever a rash appeared and he was obviously suffering from a severe attack of typhus fever. The diagnosis was later confirmed by the Weil-Felix test ; a rickettsia-agglutination test showed the infection to be of the murine type.

Treatment with aureomycin was started on the fourth day ; the drug was given at the rate of 2·5 gm. daily in divided doses, but after 36 hours the supply was exhausted and chloromycetin was given at the rate of 3·0 gm. daily for six days and then at the rate of 1·5 gm. for five days. There was a rapid improvement in his condition and about four days after the commencement of the treatment the temperature became normal.

About eight days after the onset the tongue and mouth became inflamed and soon a condition of cheilosis and an inflammation of the skin of the scrotum, perineum and perirectal region made their appearances, persisting for about three weeks. The authors did not regard these complications as being due to the drug treatment because there was no improvement, but rather the reverse, when medication ceased.

In the discussion which followed the reading of the paper Dr. J. SCHNEIDER stated that the condition was ariboflavinosis, which he and others had often observed in patients treated with aureomycin, chloromycetin and penicillin given by the mouth. The vitamin B_2 deficiency in his opinion was due to the action of the antibiotics on the intestinal flora and it could be corrected by giving riboflavin.

[This observation deserves special attention. One observer has recently suggested that the remarkable prevalence of sprue among British soldiers in the last war may have been due to an adverse influence of the sulphonamides so freely used in the treatment of bacillary dysentery ; his view was that the drug destroyed bacteria concerned in the production of vitamins in the intestine.

In the present case the treatment by antibiotics was continued far longer than is usual or necessary.] *John W. D. Megaw*

RIVOALEN, A. & PHAM-KHAC-QUANG. Étude clinique de 22 cas de typhus tropical. [**Clinical Study of 22 Cases of Tropical Typhus.**] *Rev. Méd. Française d'Extrême-Orient.* 1942, Mar., v. 20, No. 3, 302–28, 22 graphs.

ROBIN, L. A. Contribution à l'étude de la pathologie des hauts-plateaux du Sud-Annam : le pseudo-typhus tropical. [**" Pseudo Tropical Typhus " in the Uplands of South Annam.**] *Rev. Méd. Française d'Extrême-Orient.* 1941, Sept.–Oct., v. 19, No. 8, 1094–100.

ROBIN, L. A. Fièvres typho-exanthématiques indochinoises : virulence et ulcération primaire (étude expérimentale). [**Experimental Study of Virulence and Primary Ulceration in " Tropical Pseudo-Typhus " of Indo-China.**] *Rev. Méd. Française d'Extrême-Orient.* 1942, Oct.–Nov.–Dec., v. 20, Nos. 8, 9 & 10, 1077–84.

CHABAUD, H. E. & MORIN, H. G. S. Sur un cas de " pseudo-typhus tropical " (contamination expérimentale par voie buccale). [**A Case of " Pseudo Tropical Typhus " resulting from Oral Laboratory Infection.**] *Rev. Méd. Française d'Extrême-Orient.* 1941, Sept.–Oct., v. 19, No. 8, 1088–93, 2 charts.

ROBIN, L. A. Le chien domestique réservoir de virus du typhus tropical ? [**Is the Dog a Domestic Reservoir of Mite-borne Typhus ?**] *Rev. Méd. Française d'Extrême-Orient.* 1942, Oct.–Nov.–Dec., v. 20, Nos. 8, 9 & 10, 1254–8.

BRUNEAU, J. & NGUYEN-DINH-DIEP. Une épidémie de " scrub typhus " à Sonla. [**An Epidemic of Scrub Typhus at Sonla.**] *Rev. Méd. Française d'Extrême-Orient.* 1942, Mar., v. 20, No. 3, 293–301, 28 graphs & 1 plan.

LALOUEL, J. Premier essai de culture sur oeufs des rickettsies du scrub-typhus du Sud-Annam. [**A First Attempt at Yolk-Sac Culture of Scrub Typhus Rickettsiae.**] *Méd. Trop.* Marseilles. 1949, Nov.–Dec., v. 9, No. 6, 979–84, 4 graphs.

Starting from infected pleural exudate of a guineapig of the 15th passage of a strain of *Rickettsia orientalis*, isolated from a patient in South Annam, yolk-sac cultures were made and maintained through three passages. All the

five eggs employed in the attempted fourth passage were found to be contaminated. It is stated that the eggs available in Annam are very often contaminated by organisms of the *Salmonella* and *Pasteurella* groups. The strain during the three egg passages recovered some of the virulence that had been lost during the guineapig passages. *John W. D. Megaw*

O'Connor, J. L. & McDonald, Jean M. **Excretion of Specific Antigen in the Urine in Tsutsugamushi Disease (Scrub Typhus).** *Brit. J. Exper. Path.* 1950, Feb., v. 31, No. 1, 51–64, 4 figs. [15 refs.]

This paper is of a highly technical nature ; it must be read in the original form by those interested in methods of estimating the quantity of specific antigens contained in the body fluids of patients suffering from infectious diseases.

The importance of the subject is that the antigens can be detected at a very early stage of the illness ; for example in the present study the antigens of scrub typhus were found in significant quantities on the first day of the disease, and it is suggested by the authors that they may have been detectable even before the onset.

The output of the antigen in the urine is very irregular ; it is said to be usually high in the first few days, falling rapidly and again rising between the seventh and 12th days.

The irregularity of the output is shown by one example in which the quantities in mgm./ml. found on the first and following nine days of the illness were as follows : 0·43 : 0·11 : 0·07 : 0·27 : 0·08 : 0·11 : 0·21 : 0·02 : 0·03 : 0·05.

The titration of the antigen was carried out by finding how much urine was needed to inhibit the agglutination of suspensions of fowl erythrocytes which had been sensitized to a known degree of agglutinability by treatment with the specific antiserum.

The methods of preparing the erythrocyte suspensions and the standardized antigens are described ; the latter consisted of the specific polysaccharides obtained from cultures of *Proteus XK*.

The test appears to be specific ; negative results were obtained with the urine of healthy persons and of three patients suffering from murine typhus, but the authors have not yet been able to apply the test in cases of leptospirosis and rat-bite fever in which there is a Weil-Felix response of the *OXK* type.

[The test will have to be greatly simplified before being generally available as a diagnostic method.] *John W. D. Megaw*

Rao, G. S. **Brief Notes on Two Cases of Scrub Typhus Fever with Unusual Neurological Signs.** *Indian Med. Gaz.* 1950, Mar., v. 85, No. 3, 103–5.

One of the patients, after six days of low remittent fever, complained of numbness of the tongue and difficulty in articulation.

On the 13th day he was found to have hemiparesis of the right side and slurring speech. The temperature fell to normal on the 21st day, when the patient was still apathetic. A month later his condition was normal except for very slight slurring of speech.

The diagnosis of scrub typhus was confirmed by a rising and falling Weil-Felix reaction of the *Proteus OXK* type.

The other patient had remittent fever lasting 16 days ; a fortnight after defervescence he became apathetic and lachrymose, and refused to speak. There was incontinence of urine and faeces. The plantar reflexes were of the extensor type and there was ankle clonus on both sides. There was a gradual improvement, and within a month the patient was rapidly convalescing.

The *OXK* titre was 1–100 on the eighth day of the fever; it rose to 1–500 on the 13th day, was nil three weeks later, and again rose to 1–500 in the fifth week. *John W. D. Megaw*

HENDERSON, R. R., VAN SOMEREN, R. K. A. & ROBERTSON, K. E. R. **Aureomycin in Tick Typhus. A Note of its Use in Four Cases.** *East African Med. J.* 1950, Apr., v. 27, No. 4, 149–53.

Aureomycin was found effective in each of the four cases of tick typhus in Kenya described in the paper. Nausea and sometimes vomiting occurred, but did not interfere with the treatment.

Owing to shortage of the drug one of the patients was given 0·5 gm. in 10 cc. sterile water intramuscularly; this caused very severe local pain and vomiting; a similar injection to which 1·0 cc. of 5 per cent. novocaine solution was added again caused very severe pain, and treatment by the mouth was therefore given. The pain after injection lasted four days.

John W. D. Megaw

HAVENS, F. Z., Jr. & STICKNEY, J. M. **Rocky Mountain Spotted Fever successfully treated with Aureomycin: Report of Case.** *Proc. Staff Meetings Mayo Clinic.* 1950, June 7, v. 25, No. 12, 338–42, 1 fig.

A case from Minnesota.

GEAR, J. H. S., WOLSTENHOLME, B. & CORT, A. **Q Fever. Serological Evidence of the Occurrence of a Case in South Africa.** *South African Med. J.* 1950, June 3, v. 24, No. 22, 409–11. [12 refs.]

The authors report the occurrence of a positive complement-fixation reaction for Q fever at a titre of 1–25 in a patient in Western Transvaal.

The patient had suffered from several attacks of fever during the previous three months; the earliest of these was diagnosed as atypical pneumonia and in retrospect conformed to the picture of Q fever. The latest attack appeared to respond to treatment with aureomycin, but, as the authors point out, relapsing forms of Q fever have not been described. In any case the positive reaction combined with negative responses to tests for relapsing fever and the three fevers of the typhus group known to occur in the region strongly suggests that Q fever exists in South Africa. *John W. D. Megaw*

YELLOW FEVER

CAUSEY, O. R., KUMM, H. W. & LAEMMERT, H. W., Jr. **Dispersion of Forest Mosquitoes in Brazil: Further Studies.** *Amer. J. Trop. Med.* 1950, Mar., v. 30, No. 2, 301–12, 4 figs.

The following is the author's summary:—

"Further studies of the dispersion of sylvan mosquitoes marked with bronzing powders confirm and extend the observations previously reported. Using the same technique, but searching over a wider area, *Haemagogus spegazzinii*, perhaps the most important transmitter of jungle yellow fever in Brazil, was recaptured as far as 11·5 kilometers from the point of release, and *Aëdes leucocelaenus*, another efficient vector, was recovered up to 5·7 kilometers away. Out of a total of 7,624 marked *H. spegazzinii* released, 98 or 1·3 per cent., were recaptured. Other species of mosquitoes recovered at long

distances were *A. serratus* at 11·5 kilometers, *Psorophora ferox* at 10·8 kilometers, *Wyeomyia* sp. at 5·7 kilometers, *A. terrens* at 5·6 kilometers, and *Chagasia* sp. at 2·3 kilometers. The longest survival so far recorded is that of *P. ferox*, a specimen of which was found 55 days after release. In view of these findings, it seems logical to suspect that yellow fever virus may be disseminated by the movement of insect vectors in regions of small residual forests, surrounded by open pasture land and cultivated fields, as typified by the country in western Minas Gerais.

" An additional series of experiments to determine the influence of wind on this movement showed that forest mosquitoes travel in the directions of the prevailing winds during the hours of daylight. On no occasion was a marked specimen recaptured in a forest which could have been reached only by flight against the wind."

See also p. 951, BRUCE-CHWATT, **Recent Studies on Insect Vectors of Yellow Fever and Malaria in British West Africa.**

DENGUE AND ALLIED FEVERS

FLORIO, L., MILLER, Mabel S. & MUGRAGE, E. R. **Colorado Tick Fever. Isolation of the Virus from *Dermacentor andersoni* in Nature and a Laboratory Study of the Transmission of the Virus in the Tick.** *J. Immunology.* 1950, Apr., v. 64, No. 4, 257–63. [11 refs.]

This paper contains full details of the experiments on the strength of which two of the authors have already reported the isolation of the virus of Colorado tick fever from nine out of ten pools of ticks (*Dermacentor andersoni*) collected from areas in Denver where the disease is endemic [see this *Bulletin*, 1948, v. 45, 512].

Transovarian infection was found to occur among the offspring of ticks infected by biting infected hamsters.

The exhaustive nature of the investigation is shown by the fact that about 300 hamsters were used in the experiments.

By neutralization tests the authors confirmed their previous observation that a pronounced fall in the leucocyte count of inoculated hamsters is clear evidence of infection by the virus of Colorado tick fever. *John W. D. Megaw*

FLORIO, L., MILLER, Mabel S. & MUGRAGE, E. R. **Colorado Tick Fever. Isolations of Virus from *Dermacentor variabilis* obtained from Long Island, New York, with Immunological Comparisons between Eastern and Western Strains.** *J. Immunology.* 1950, Apr., v. 64, No. 4, 265–72.

This paper, like its immediate predecessor, supplies details of experiments, results of which have already been published [see this *Bulletin*, 1948, v. 45, 512]. From dog-ticks (*Dermacentor variabilis*) collected in Long Island, New York, the authors have isolated three strains of a virus which they conclude to be the virus of Colorado tick fever or " a very closely related virus immunologically ".

Colorado tick fever has never been reported from Long Island, but the authors state that it " is probably occurring in humans on Long Island, but is unrecognized ".

Although very large numbers of hamsters were employed in the study of the three strains of virus, the original isolation of the strains was made from a relatively small number of ticks : the first strain was obtained from a hamster

on which a single pair of ticks had been allowed to feed ; the other two strains were isolated from two out of four pools consisting of about 20 ticks each.

John W. D. Megaw

RABIES

ZLOTNIK, I. **A Severe Outbreak of Rabies in Israel.** *Veteran.* 1949, v. 1, 127–9. [Summary taken from *Vet. Bull.* 1950, Mar., v. 20, No. 3, 139. Signed G. V. LAUGIER.]

By the 1st of April, 1948, rabies reached endemic proportions in Israel with 14 deaths among human beings and considerable losses among cattle. It was ascribed to numerous jackals acting as a reservoir, and to homeless dogs left by Arab refugees. Eradication of jackals presents difficulties owing to opposition from agriculturists and to infiltration from frontiers. Diagnosis is carried out solely by the Central Veterinary Laboratory and is based on the demonstration of Negri bodies and inoculation test on white mice. In carnivores it is observed that the size and number of Negri bodies increase with the length of illness. Control measures comprise destruction of jackals and stray dogs, licensing and compulsory vaccination of all other dogs.

TUNÇMAN, Z. M. Porsuk—blaireau isirmasindan ileri gelen nadir bir kuduz vak'asi. [**A Rare Case of Hydrophobia due to Bite of Badger.**] *Türk Tip Cemiyeti Mecmuasi.* 1949, Apr., v. 15, No. 4. [In Turkish 209–10. English summary 18.]

TUNÇMAN, Z. M. Merkep tarafindan isirilmis dana kuduzu vak'asi. [**A Case of a Calf Hydrophobia due to a Bite of an Ass.**] *Türk Tip Cemiyeti Mecmuasi.* 1949, Apr., v. 15, No. 4. [In Turkish 210. English summary 18.]

PIRINGER, W. A. & HELL, H. M. Die Tollwutschutzimpfung nach HEMPT. [**Hempt's Method of Vaccination against Rabies.**] *Ztschr. f. Hyg. u. Infektionskr.* 1950, Mar. 22, v. 130, No. 6, 543–64. [18 refs.]

This is a report of the Vienna Antirabic Institute covering the period from 1943 to 1947. In 1943, for reasons of convenience, the Vienna Institute changed over from Semple's method to Hempt's method of producing rabies vaccine, as the latter requires only a reduced course consisting of six daily injections to be followed by a seventh four weeks later. A description of Hempt's method of vaccine production is given [information regarding the final phenol concentration of the product is lacking, and no reference to any kind of potency testing is made].

Nine hundred and fifty-five persons have been treated in the above-mentioned period. Out of these one person died 30 days after a superficial facial bite and 20 days after treatment was begun. One unvaccinated veterinarian, who had not been bitten but had a wound on his thumb at the time, died of rabies 60 days after dealing with a dog that developed the disease a few days later.

A sharp rise in rabies incidence in Austria has been observed in the first two post-war years, and is ascribed to the absence of adequate control measures during that period.

C. R. Klimt

KOPROWSKI, H. & LEBELL, I. **The Presence of Complement-Fixing Antibodies against Brain Tissue in Sera of Persons who had received Antirabies Vaccine Treatment.** *Amer. J. Hyg.* 1950, May, v. 51, No. 3, 292–9. [19 refs.]

Sera of 50 persons vaccinated against rabies obtained before and at regular intervals after commencement of vaccination, were tested for normal brain

antibodies. The antigen for the complement-fixation test was prepared partly by the technique of CASALS and PALACIOS [*Bulletin of Hygiene*, 1942, v. 17, 444] and partly by that developed by DE BOER and COX [*ibid*, 1947, v. 22, 418] from normal human or rabbit brain. None of the 16 persons who had received a course lasting seven days showed antibrain antibodies at any time, whereas 17 (50 per cent.) out of the 34 who had received a course of 14 days showed antibody titres above 1 : 4. No pre-vaccination titres were observed, except in the case of one person who had previously received antirabies treatment. In spite of high titres none of these persons showed any symptoms.

A second study was made with sera obtained from three patients with neurological complications after antirabies treatment. High brain antibody titres were found in two of these, and lower antibody levels in one. While in the first two cases symptoms appeared on the day of the 14th and 12th injection respectively, in the last case symptoms appeared only three and a half weeks after termination of treatment. *C. R. Klimt*

DOGRA, J. R. **Studies on Antirabic Vaccines. IV. A Single Dose Prophylactic Canine Vaccine.** *Indian J. Med. Sci.* 1950, June, v. 4, No. 6, 245–9.

A phenol-killed antirabic vaccine for veterinary use containing 25 per cent. sheep brain has been tested in mice and some dogs.

Habel's potency mouse test has been modified, as only one intraperitoneal injection of 0·3 cc. of a 2·5 per cent. vaccine is given, which is followed by intracerebral challenge on the 15th day thereafter. The results of these tests seem to show good protective values [the titres of the challenge viruses seem extraordinarily high, and can be directly correlated to the m.l.d. protection obtained].

Three series of tests in dogs were carried out ; the results in the immunized group were that three out of five, three out of five and one out of four contracted rabies, while the controls read as follows : two out of three, two out of three, and three out of three. These results do not seem to substantiate the conclusion of the author, which reads : " This protection afforded by a single dose vaccination is considered of a very high order." [The intracerebral challenge with fixed rabies virus of the immunity obtained in dogs is a procedure abandoned by most workers because of its almost complete lack of relationship to the natural type of exposure. Particular objection must be raised to the following two statements contained in the article : " These dogs are exposed to [natural] infection and conceivably acquire varying degrees of immunity to rabies infection. This possibly was the explanation of the irregular results obtained in the first two [dog] experiments ", and a batch of dogs was obtained and " kept under observation for a week to ensure that animals were free from rabies and other pathological conditions ".] *C. R. Klimt*

CHOLERA

FOURNIER, J. & LIEOU, Y. C. Contribution à l'étude des vibrions cholériques de Changhai. (Vibrions isolés à l'Institut Pasteur en 1939, 1940, 1941 et 1942.) [**Study of Cholera Vibrios isolated at the Pasteur Institute, Shanghai in 1939 to 1942.**] *Rev. Méd. Française d'Extrême-Orient.* 1943, Apr.–May–June–July, v. 21, Nos. 4, 5 & 6, 541–51. [20 refs.]

COLLIER, H. O. J., CAMPBELL, N. R. & FITZGERALD, M. E. H. **Vibriostatic Activity in certain Series of Pteridines.** *Nature.* 1950, June 24, 1004–5.

A number of 6 : 7-disubstituted 2 : 4-diaminopterines were prepared and tested for their vibriostatic activity by the methods described by COLLIER, HALL

and WATERHOUSE [this *Bulletin*, 1950, v. 47, 236]. The minimal concentrations of the pterines in peptone water at *p*H 7·2 were first determined which would inhibit, for 24 hours at 37°C., the growth of an inoculum of 10^3 *V. cholerae* per ml. In the series of 2 : 4-diamino-6 : 7-dialkylpterines the greatest activity was shown by the *iso*propyl compound (Serial number 0/129). The di-*sec*-butyl, the di-ethyl, and the di-*n*-propyl derivatives were slightly less active and the compounds with longer or shorter alkyl chains were far less active. In the 6 : 7 di-aryl series both the di(p-methoxyphenyl) (0/61) and the di-furyl derivative showed considerable activity. The most active compound of all tested was the 2 : 4-diamino-l'-methyl-indolo (2^1 : 3^1-6 : 7)-pteridine (II), (0/120).

When administered to mice in their diet over a period of three weeks the maximum tolerated proportions of the three most active compounds, 0/61, 0/120 and 0/129 were respectively 0·2, 0·8 and 0·8 per cent.

The vibriostatic titres of the faeces of mice to whose diets the drugs had been added were estimated by preparing serial dilutions in peptone water, autoclaving, and then inoculating with 10^3 *V. cholerae* per ml. as described by COLLIER *et al.* With pteridine 0/120 the titre was 1 in 320 to 1 in 640 when the percentage in the diet was 0·4. This figure compares with a titre of 1 in 160 when sulphaguanidine was added at the level of 4·0 per cent. of the diet. Lesser activity was shown by 0/61 and 0/129.

When 0·4 per cent. pteridine was added to the diet along with 3·6 per cent. sulphaguanidine synergic action was shown, the titres being considerably higher than with either drug alone. With 0/120 and sulphaguanidine the titre was 1 in 2,560 to 1 in 5,120.

Several of the compounds powerfully inhibited *Strep. faecalis*. This inhibitory action was overcome by pteróylglutamic acid. *John Taylor*

AMOEBIASIS AND INTESTINAL PROTOZOAL INFECTIONS

i. AMERICAN J. TROP. MED. 1950, Mar., v. 30, No. 2, 121–2. **The Amebiasis Panel. Introduction** [BROOKE, M. M., Chairman].

ii. WRIGHT, W. H. **The Public Health Status of Amebiasis in the United States, as revealed by Available Statistics.** *Amer. J. Trop. Med.* 1950, Mar., v. 30, No. 2, 123–33. Discussion [MACKIE, T. T.]. 133–4.

iii. NEWTON, W. L. **Water Treatment Measures in Control of Amebiasis.** *Ibid.* 135–8. [16 refs.] Discussion [BROOKE, M. M.] 139.

iv. SODEMAN, W. A. **Clinical Picture of Hepatic Amebiasis.** *Ibid.* 141–3. Discussion [D'ANTONI, J. S.] 144–6.

v. HUSSEY, K. L. & BROWN, H. W. **The Complement Fixation Test for Hepatic Amebiasis.** *Ibid.* 147–54. [12 refs.] Discussion [BOZICEVICH, J.] 154–7.

vi. DENNIS, E. W. **Discussion (of paper by Neal J. Conan).** *Ibid.* 159–64. [11 refs.]

vii. AMERICAN J. TROP. MED. 1950, Mar., v. 30, No. 2, 165–9. **General Discussion on Amebiasis Panel** [BOZICEVICH, J. ; HUSSEY, K. L. ; BROWN, H. W. ; KESSEL, J. F. ; REES, C. W. ; SODEMAN, W. A. ; MACKIE, T. T. ; STUNKARD, H. W. ; KOTCHER, E. ; BROOKE, M. M. ; OTTO, G. F.].

i. This number of the journal is devoted to the papers and discussions forthcoming from the " Amebiasis Panel " which met at the Annual Meeting of the

American Society of Tropical Medicine at New Orleans in December, 1948. In his opening address the chairman, M. M. BROOKE, propounded a number of the problems connected with amoebiasis which still awaited solution; he hoped that the deliberations of those contributing to the symposium, if they did not solve these, might at least clarify the existing situation.

ii. The possible effect of the return to the United States of service personnel infected overseas with *Entamoeba histolytica* caused concern after World War I. While one survey at that time [this *Bulletin*, 1924, v. 21, 422] showed no greater incidence of this parasite in ex-servicemen than in control groups, another [this *Bulletin*, 1920, v. 15, 208] suggested that it was about three times as great in troops returned from overseas as in those who had not left home bases. A comparable survey after World War II [JACOBS, WALLACE and DIAMOND, *Bull U.S. Army Med. Dept.* 1946, v. 6, 259; see this *Bulletin*, 1947, v. 44, 89] revealed a higher incidence of *E. histolytica* infection in troops who had served overseas than in home service troops; those from the China-Burma-India area showed the highest incidence of infection (20·3±3·1 per cent.), which was about twice that found among the home forces.

Owing to the varying regulations and differing nomenclature of disease obtaining in the different States of the U.S.A., as well as to their divergent standards of diagnosis, there is much inconsistency in the reports from them on the occurrence of amoebiasis, and the data available are not comparable. The confusion of the records has tended to limit the number of cases reported, rather than to exaggerate it, but in spite of inconsistencies and inaccuracies there has for some years been a steady increase in the number of recorded cases of amoebiasis and of amoebic dysentery. This increase may in part be due to greater consciousness of the disease from acquaintance with it overseas by physicians. While detailed enquiries tend to confirm the opinion that the morbidity figures do not approximate to the actual number of cases of amoebiasis which exist in the various States, the published records of mortality from amoebiasis more closely approach reality. Study of the latter shows a steady downward trend in the deaths due to amoebic infection between the years 1933 and 1946 in all areas of the U.S.A. The figures both of morbidity and of mortality have uniformly been highest throughout this period in the West South Central States (Arkansas, Louisiana, Oklahoma and Texas) and lowest in New England.

Statistics from the Veterans Administration show that for the five years before 1946 relatively few veterans were admitted to hospital for amoebiasis, but in this and the following year the number markedly rose (1945, 64 cases; 1946, 529; and 1947, 1,325).

In 1940, the National Institute of Health began, as a routine procedure, to do a complement fixation test for amoebiasis with a much improved antigen. In the succeeding seven years requests for this test have steadily increased from 142 to 2,974 *per annum*; this shows an increasing appreciation on the part of physicians of the importance of the infection, though it does not necessarily indicate a greater prevalence of the disease. The general impression is gained that in spite of the fall in the death rate attributable to amoebiasis there has been a gradual increase in the incidence of the infection, but that this increase is not due to the return to the U.S. of troops infected overseas during the recent world war.

In the discussion which followed, MACKIE cited his own and others' experience of the inadequacy of health department statistics as a guide to the incidence of amoebiasis. He condemned the almost universal practice of discharging crude sewage into streams as conducive to the dissemination of the infection; and he felt that the importance of infected food-handlers, flies, and the use of sewage sludge as fertilizer in the spread of the infection merited consideration.

iii. The treatment of water supplies to remove or to destroy cysts [of *Entamoeba histolytica*] falls into two classes : that of large-scale municipal supplies and that of small-scale, portable, or individual supplies. The measure normally adopted in the case of the former first of all is sedimentation, sometimes with the addition of a flocculating chemical ; plain sedimentation is of little value in removing cysts, which settle in clear distilled water at the rate of only one inch an hour, but an alum flocculation process producing a rapidly settling floc is much more effective. Rapid gravity sand filtration, which normally follows the sedimentation process, is probably very effective in removing cysts. The usual chemical treatments, and especially ordinary chlorination, which then commonly follow, are ineffective in killing cysts. Superchlorination, with subsequent removal of the excess chlorine, may be effective in doing this ; ozonization is probably even more so. The greatest practicable protection against water-borne infection on the large scale, therefore, at present is the mechanical measure of sand filtration.

In the case of small scale, portable, or individual supplies, serving camps, canteens or similar limited units, chemical coagulation with detention for at least two hours would be useful, and this should be followed by filtration under pressure. A portable sand filter is inadequate, as its effectiveness in removing cysts is inversely proportional to the speed with which water containing them traverses such a filter ; portable filters of diatomaceous earth, however, are effective in removing cysts from water passing through it rapidly (30–40 gallons a minute). Chemical treatments (hypochlorites, halazone, succinchlorimide and chloramines) to be effective must give a high concentration of available chlorine in the form of hypochlorous acid. Iodine compounds have shown some promise as destroyers of cysts, and have the advantage over chlorine compounds that their action is not influenced to the same extent by alterations in *p*H, and they do not produce so unpleasant a taste. Synthetic detergents of the cationic type are effective only in concentrations too high for a drinking water ; those of the anionic type are ineffective. Bromine is of doubtful value, and the use of ultraviolet irradiation is impracticable on any but the smallest scale. Thus in the case of limited water supplies the use of mechanical filtration, under pressure through diatomaceous earth, after preliminary sedimentation, is the method of choice if the supply is large enough to warrant it ; if it is not, iodine is the chemical sterilizing agent of choice.

[Reference is not made to the effect of storage alone ; cysts survive in water for periods inversely proportional to the temperature, and even at lowest normal temperatures they do not survive more than a couple of weeks. See also MORTON, this *Bulletin*, 1948, v. 45, 377.]

iv. Hepatic amoebiasis should be detected long before it reaches an advanced stage, though patients occasionally do not even seek advice until a large abscess is on the point of rupturing, as early diagnosis facilitates a cure by simple medicinal treatment. It is only with the very earliest stages of hepatic amoebiasis that the author of this paper is at present concerned.

Enlargement and tenderness of the liver were found rather frequently in children suffering from intestinal amoebiasis ; these signs were associated with skin changes especially of the face, which resembled a fading sun tan ; in children so affected changes were also observed in personality and in reaction to environment. Dermatological and psychological manifestations thus may be observed in a very early stage of liver amoebiasis ; they vanish on specific treatment of the amoebic infection.

In adults the earliest evidence of hepatic amoebiasis is enlargement and tenderness of the liver, without fever or leucocytosis. These signs, in association with a proven intestinal infection, warrant a presumptive diagnosis which is confirmed by a prompt response to specific anti-amoebic treatment. The

actual histo-pathology of the liver in such cases is not clear ; liver biopsy in one case yielded parasites, but it is not certain that an advanced amoebic hepatitis or abscess would have followed. Early diagnosis, and consequently treatment while the patient is still ambulant, minimizes the risk of drug reaction and reduces the incidence of more serious developments with their associated mortality.

Amoebic liver disease causes an insular type of lesion in the liver, and leaves sufficient normal liver tissue adequately to carry on its function. Liver function tests therefore do not afford help in the specific diagnosis of amoebiasis of the liver, but they do help in excluding other types of liver disease.

v. After describing the history of the adaptation of the complement deviation test for amoebiasis since its inception in 1914, the authors report the results of examination of sera from 275 patients with intestinal or hepatic amoebiasis and other clinically related conditions. The materials used were a commercially produced *Entamoeba histolytica* antigen, a commercially produced lyophilized guineapig complement and an anti-sheep haemolysin from rabbits, and a stock sheep red cell suspension. The aim was to evaluate the complement fixation test in amoebiasis when performed with reagents readily obtainable in quantity.

Of the sera from 124 persons with an intestinal *E. histolytica* infestation, who showed symptoms of varying degrees of severity, 121 (97·6 per cent.) gave a negative complement fixation test while only 3 (2·4 per cent.) gave a positive test. Of the sera from 116 uninfected controls 111 (95·7 per cent.) gave a negative test and 5 (4·3 per cent.) a positive test. Of the sera from 12 cases of undoubted hepatic amoebiasis 10 (83·4 per cent.) gave a positive complement fixation test and 2 (16·6 per cent.) gave a negative test. Five sera obtained from patients with a probable hepatic amoebiasis gave 4 positive (80 per cent.) and 1 negative (20 per cent.) complement fixation tests. It thus appears that whereas the complement fixation test is of no value in proving the presence of an intestinal *E. histolytica* infection the test is positive in the majority of cases of hepatic amoebiasis which were diagnosed clinically and on the effect of specific drug treatment.

Complement fixation tests performed on the sera of 49 other patients suffering from a variety of conditions, including liver disease in the form of infective hepatitis, carcinoma of the liver, cirrhosis and hydatid disease, all gave negative readings ; but sera from four patients, suffering from clonorchiasis, from malaria, from proctitis and from a possible chromoblastomycosis respectively, gave false positive tests. In the case of the first two of these the reaction was one plus, in that of the second two plus, and in that of the third three plus.

Re-examination at the Army Medical School of portions of the sera examined gave closely agreeing results in 70 per cent. of the 52 positive sera, slight divergence in 13 per cent. of them, and marked divergence in 17 per cent. ; the antigen used at the Army Medical School was from a different batch, and there is some variation in sensitivity in various batches of the same antigen which might account for the differences.

The general conclusion is reached that with the commercial antigen and the technique used the complement fixation test is of diagnostic value in hepatic amoebiasis, in that a positive test is of significance though a negative test may be obtained in proven cases. This test is of no value in the diagnosis of intestinal amoebiasis.

In discussion John Bozicevich stated that he had done over 13,000 complement fixation tests for amoebiasis since 1942. He considered that the differences in the results obtained from the two laboratories referred to by the previous authors were attributable to differences in technique and in the antigens employed. He described the technique employed at the Army Medical Centre,

and pointed out that the preceding authors had used a period of fixation of only 4 hours, instead of the overnight fixation recommended for other fixation tests. Longer fixation, with changes in the dilution of serum and in the concentration of antigen, will yield more satisfactory results; with such modifications he found the complement fixation test to give results in much closer agreement with the results of the stool examinations. For example, of 59 persons with *E. histolytica* in their stools only 9 gave negative complement fixation tests while 50 gave positive fixation tests. Two of the 9 patients whose sera gave negative tests had had a specific treatment for their infections, and it has been observed that successful treatment results in a progressive fall in the antibody titre.

The use of a polyvalent antigen greatly increases the specificity of the complement fixation test, as differences exist in antigenic power between races of *E. histolytica*. The sera of 16 persons harbouring a small race of *E. histolytica* gave negative complement fixation tests, but the majority of those from patients harbouring a large race of the parasite give positive fixation tests.

vi. *Entamoeba histolytica* has only two significant forms in its life cycle, the invasive trophozoite and the passive cyst; lesions of amoebiasis are always due to the invasion of tissue by the former, and the aim of chemotherapy is its destruction. The cysts are discharged to the exterior; though their discovery is of diagnostic importance their destruction is a problem of sanitation and not one of chemotherapy. Amoebiasis is an ubiquitous and protean condition, it is not an exotic tropical one; it is doubtful if acute dysentery is any more typical of amoebiasis than acute staphylococcal bacteraemia is characteristic of a human staphylococcal infection. Though marked hepatic involvement probably does not occur in more than two per cent. of those harbouring a bowel infection with *E. histolytica*, some degree of secondary involvement of the liver is common; 53 per cent. of 94 patients had enlargement of the liver, but only 16 per cent. of this series had a palpable colon. Amoebiasis can essentially be regarded as a focal infection; it is characterized by ulcerative foci in the large bowel with a tendency to embolism elsewhere, but the primary foci may be insignificant in number and size and so cause no clinical manifestasions of their presence. For example, BANKER [this *Bulletin*, 1948, v. 45, 338] found that only 40 per cent. of 184 patients with an amoebic liver abscess had suffered any dysenteric symptoms. Such data indicate that a hepatic amoebic infection is a probability when parasites are found in the stools, especially if the complement fixation test is positive, and that treatment should be directed to it as well as to the bowel infection.

The desiderata in an amoebicidal drug are (1) amoebicidal potency, either directly or after metabolic change in the body, (2) absence of toxicity to the host, (3) assimilability and distribution in the body to all sites of infection in effective concentration, and (4) sufficient prolongation of action to produce a therapeutic effect. Drugs given orally are unlikely to reach the large bowel in adequate concentration for a local action if absorbed in transit, and that portion absorbed can rarely be found in significant amount in the wall of the large bowel. An actively amoebicidal drug may be inactivated by conjugation or by acetylation at the site of a liver infection. Slowly absorbed drugs, given orally, though reaching the large bowel in effective concentration, will not achieve an effective concentration at the secondary foci of infection. The treatment of the primary foci in the bowel is essentially local, and that of the extra-intestinal lesions systemic. For the former the wide range of drugs in common use may be further enlarged by some new preparations now under trial and showing promise. For the latter to emetine can now be added chloroquine, which reaches its highest concentration in the liver and which is excreted from the body very slowly. It is a potent drug in systemic amoebiasis, which

can safely be given in effective dosage, and it is free from the undesirable side effects due to emetine, which also may produce drug resistance.

The rational treatment of amoebiasis thus involves the use of an effective amoebicide for local treatment of the primary intestinal foci, and the concomitant use of chloroquine diphosphate to destroy the extra-intestinal parasites.

vii. John Bozicevich considered the complement fixation test to be a guide in the diagnosis of amoebiasis which should be employed in conjunction with stool examinations before specific treatment is given. Efficient examination of the stools is not easy; it requires long practice and much skill, and even after these have been acquired some amoebae cannot be specifically identified.

H. W. Brown said that changes of the antigen and in the technique for the performance of the complement deviation test were being made at short intervals at the research institutes in an effort to improve the procedure. As a practising physician without special facilities he was satisfied with a simply performed test with readily procurable materials, which would give positive reactions in cases of hepatic amoebiasis and negative ones with the intestinal infections. While a positive complement fixation test in association with a microscopically proven intestinal infection is highly suggestive of amoebic hepatitis, clinical findings must be given their due weight in the final resort.

John F. Kessel had found the antigens he had used in the past for complement fixation tests in amoebiasis imperfect, and he now referred sera from his cases to the National Institutes of Health for report.

Chas. W. Kees stated that no accurate diagnosis was possible on purgative stools. Vegetative *E. coli* may be mistaken for *E. histolytica*, even by the expert. The four-nucleate cysts are the only forms susceptible to precise diagnosis.

W. A. Sodeman found nobody to agree on how the complement fixation test should be performed or on its interpretation in the diagnosis of amoebiasis. It was not remarkable that the physicians tended to disregard them all. Even when *E. histolytica* was found in the stools it might not necessarily be the cause of the patient's symptoms. It was the physician's duty to consider all the laboratory data and to correlate them to the physical findings.

T. T. Mackie said that diagnosis was based on the discovery in fresh specimens of stool of organisms which displayed characteristic morphological features. Motile amoebae with marked distinction between the ectoplasm and the endoplasm and with engorged red cells, he regarded as *E. histolytica*.

Horace W. Stunkard thought that Brumpt's technique for the rectal infection of young kittens would reveal within 48 hours whether an amoeba was *E. histolytica* or not.

Emil Kotcher said that the Mississippi State Board of Health, with which he was associated, in 1947 began a new system for reporting morbidity due to amoebiasis. The name and the address of the infected person were reported, and as a result of this innovation far fewer cases were recorded. Before this it had been observed that most of the cases were reported from one community by physicians at a clinic doing its own laboratory work. Re-examination of the specimens at the State Hygienic Laboratory did not corroborate the findings of this private laboratory.

M. M. Brooke confirmed the unreliability of the records from the private laboratories referred to by the previous speaker. The reports were based on examination of purged specimens, and any trophic amoebae seen were regarded as *E. histolytica*. A series of persons doing laboratory examinations in the area were given numbered specimens of stool and most of them failed to identify the findings consistently or correctly. The high reported incidence of amoebiasis was, therefore, due to misdiagnosis.

Gilbert F. OTTO had not found any particular technique of stool examination wholly satisfactory; the least satisfactory and most time-consuming of all was the cultural. Various methods of transference of parasites from one host to the next had been referred to, but it would be well to consider the probable means of transference as opposed to the possible. Flies undoubtedly can carry the infection and may do so occasionally; infected drinking water may be of importance, and the rôle of the food-handler is difficult to assess. The importance of any of these three means of transference is minor in comparison with the obvious gross faecal contamination of premises to be seen both in urban and in rural districts in the South. Reference to the familial incidence of infection with *E. histolytica* might suggest that the mother, who is the food-handler, may be responsible; but similar familial infection occurs with hookworm and ascaris. The basic method of distribution of these infections is faecal contamination; the other methods referred to merely augment this.

A. R. D. Adams

LINCICOME, D. R., THIEDE, W. H. & CARPENTER, Elizabeth. **An Evaluation of the Influence of World War II on the Incidence of Amebiasis.** *Amer. J. Trop. Med.* 1950, Mar., v. 30, No. 2, 171–9. (63 refs.)

Fears have been expressed that *Entamoeba histolytica* infections would become more prevalent in the United States as a result of the large-scale re-introduction of the parasite in service personnel infected overseas during the late war. Now, four years after its end, it is appropriate to investigate the position. In January, 1948, a study of the incidence of intestinal *E. histolytica* infestation in over 1,100 students at the University of Wisconsin was undertaken; the results are compared with those recorded by various workers in groups of post-war veterans, of service personnel under combat conditions, and of pre-war student populations.

The methods of examination adopted by the authors were a single stool examination by (1) direct film stained with iodine, (2) Faust's zinc sulphate concentration method, and (3) a fixed haemotoxylin-stained film. The fact that this single examination discloses not more than 30 or 40 per cent. of the positive cases is appreciated, but the figures cited for the purpose of comparison were similarly based.

The recorded findings of a large number of workers in this sphere are listed in tables; it emerges that the reported incidence of *E. histolytica* infection in some 50,000 members of the U.S. military forces engaged in domestic and overseas service during the war averaged 14·7 per cent., the extremes in individual records ranging from 0·48 to 100 per cent. in groups of much differing size. Of the 1,110 students examined by the authors, 3·5 per cent. harboured *E. histolytica* bowel infections, the highest incidence being 4·5 per cent. in veterans with overseas service, and the lowest 1·6 per cent. in those with no war service. Among those with war service the highest incidences were 10·6 per cent. in 47 students from the Mediterranean, and 8·5 from the China-Burma-India theatres; the lowest were 0 per cent. in the Greenland-Iceland-Alaska and 1·4 per cent. in the Britain and Continental European theatres outside the Mediterranean area. Non-service students (11,236) drawn from several States of the Union, as recorded by several workers between 1931 and 1944, showed an incidence of 4·9 per cent. infection with *E. histolytica*.

Various computations of the overall incidence of *E. histolytica* infection in the U.S. have ranged from 10 per cent. by CRAIG in 1926 (this *Bulletin*, 1926, v. 23, 790) to 20 per cent. by FAUST in 1942 (*ibid.*, 1942, v. 39, 554); so the figures disclosed by this study reveal no significant differences from the computed rate as a sequel to the war.

A. R. D. Adams

CARRERA, G. M. **Acid Phosphatase Activity in the Intestinal Wall in Experimental Amebic Colitis.** *Proc. Soc. Exper. Biol. & Med.* 1950, Apr., v. 73, No. 4, 682, 1 fig.

The author with CHANGUS has already demonstrated acid phosphatase activity in *Entamoeba histolytica* by means of Gomori's histo-chemical technique [this *Bulletin*, 1949, v. 46, 144].

He has now studied this activity in the tissues in experimental amoebic colitis in guineapigs heavily inoculated with over 200,000 trophozoites (Tulane strain XXII) by the intra-ileal method. The amoebae were grown on Balamuth's medium [this *Bulletin*, 1947, v. 44, 1066].

After 4 to 7 days the animals were killed and extensive lesions in the caecum were studied by Gomori's method. Duplicate specimens were treated in the same way, to serve as controls, but the glycerophosphate substrate was omitted from the incubating solution.

Very heavy black (lead sulphide) precipitate was seen in and around the areas of amoebic invasion and also in isolated amoebae some distance away: no demonstrable enzymatic activity was seen in the surrounding host tissue. Foci of the black precipitate were also seen which did not correspond to the amoebae, but were always near them. It is suggested that these might have been fragments of amoebic protoplasm or small microorganisms from the lesions.

In the areas unaffected by the amoebae, no such foci of phosphatase activity were evident and all the controls were negative.

The findings described are well illustrated in a photomicrograph.

The author concludes that the precipitate does in fact represent acid phosphate activity: the very strong reaction in the immediate environment of the amoebae, as well as in the isolated amoebae themselves, confirm the impression that *E. histolytica* has a high concentration of acid phosphatase.

H. J. O'D. Burke-Gaffney

CORCOS, A. Psychologie de l'amibien chronique en Tunisie. Conséquences thérapeutiques. [**Psychological Aspects of Chronic Amoebiasis in Tunisia and its Therapeutic Implications.**] *Bull. Soc. Path. Exot.* 1950, v. 43, Nos. 5/6, 267–70.

Intestinal amoebiasis is very prevalent in Tunisia, where it may be the cause of various psychiatric troubles.

In those normally of stable mental equilibrium it may result in irascibility, depression, and a morbid interest in the condition. In those tending normally to mental instability, usually urbanized young women, often Jewish, there is also often wasting due to self-imposed dietary restriction. Various suggestions are made as to how these cases should be dealt with. *A. R. D. Adams*

TÔN-THÂT-TÙNG. Deux cas d'amibiase cutanée. [**Two Cases of Cutaneous Amoebiasis.**] *Rev. Méd. Française d'Extrême-Orient.* 1942, Oct.–Nov.–Dec., v. 20, Nos. 8, 9 & 10, 1155–7.

HUARD, P. & NGUYEN-XUÂN-NGUYEN. Un nouveau cas d'amibiase-cutanée. [**A New Case of Cutaneous Amoebiasis.**] *Rev. Méd. Française d'Extrême-Orient.* 1942, Oct.–Nov.–Dec., v. 20, Nos. 8, 9 & 10, 1187–8, 1 fig.

RIVOALEN, A. & PHAM-KHAC-QUANG. Les pseudo-cancers intestinaux d'origine amibienne. [**Pseudo-Cancerous Intestinal Growths of Amoebic Origin.**] *Rev. Méd. Française d'Extrême-Orient.* 1941, May–June, v. 19, Nos. 5/6, 422–40. [40 refs.]

An account of 26 cases.

RAVINA, A., GUÉRIN, P., PÉCHER, Y. & CLAVEL, B. Abcés amibien du foie, à évolution mortelle, survenu chez un homme rapatrié d'Indochine depuis vingt moins et n'ayant présenté aucun antécédent dysentérique appréciable. Absence de lésions intestinales à l'autopsie. [**Fatal Amoebic Liver Abscess without History or Intestinal Signs of Dysentery occurring Twenty Months after Departure from Indo-China.**] *Bull. et Mém. Soc. Méd. Hôpit. de Paris.* 1950, Nos. 19/20, 974–5.

VALCKE, G. Amibiase hépatique. [**Hepatic Amoebiasis.**] *Ann. Soc. Belge de Méd. Trop.* 1950, Mar. 31, v. 30, No. 1, 121–9.

Emetine is given with excessive caution in the Belgian Congo ; consequently it often fails in its purpose, and recrudescences of dysentery and an increased number of cases of amoebic hepatitis result. Restriction in dosage may be due to the fact that the drug is given to ambulatory patients. In Antwerp, since 1933, certain practices have been observed when emetine is used : (1) the patient is admitted to hospital during treatment, and is kept recumbent for some hours after each injection, and (2) the total dosage is from 640 to 720 mgm.; the first day two injections each of 40 mgm. are given deeply intramuscularly, subsequently a single daily injection of 80 mgm. is similarly given. In the event of there being intolerance the drug is injected slowly intravenously. Emetine should not be injected subcutaneously as this causes pain. In unusually heavy persons doses of 100 mgm. may be given, the total dosage approximating to a scale of 10 mgm. of emetine for each kgm. of bodyweight.

Emetine treatment is combined with the use of an iodo-oxyquinoline derivative by the mouth, and sometimes with stovarsol, though the latter may damage the liver ; relapses may occur after these courses. Relapse is less frequent when penicillin and sulphaguánidine are also given.

Amoebic hepatitis is difficult to diagnose ; the author treats specifically with emetine any hepatitis, however mild, which does not respond to simple treatment when there is a possibility of previous dysentery ; this forestalls complications in cases of amoebiasis. He cites in detail and at length five cases, of 44 cases treated by him during 1948–1949, to point his contentions [in only one of these five was the presence of an *Entamoeba histolytica* infestation in the gut definitely established]. *A. R. D. Adams*

BONNIN, H. Les nouveaux traitements de l'amibiase. [**The Modern Treatment of Amoebiasis.**] *J. Méd. de Bordeaux.* 1950, Apr., v. 127, No. 4, 233–45.

Amoebic disease can be divided into : (1) periods of dysentery or dysenteric diarrhoea due to destructive invasion of the colon by amoebae, and (2) a state of chronic colitis, with periodic exacerbations and a variety of symptoms due to organic or functional injury following an amoebic infection.

In considering the treatment of the first of the two clinical syndromes of amoebic disease the author states that emetine hydrochloride, the drug classically used in the treatment of acute dysentery, must be stored in coloured ampoules on ice, because light and heat alter it ; such alterations may explain the apparent inactivity of the drug. Emetine given parenterally remains the classical treatment for the relief of the dysenteric state, but it does not destroy parasites in the lumen of the bowel ; it is unwarrantable to give repeated courses of emetine injections in a vain endeavour to destroy these, as is so frequently done. As emetine is a cumulative poison a total dosage of one centigramme for each kilogramme of the patient's weight should not be exceeded. Cardiac tonics, such as camphor, strychnine or Vitamin B1, should be given with each injection, and the arterial tension must be watched daily

during emetine treatment. The manifestations of emetine poisoning are numerous, but they are rarely encountered except as a result of repeated ill-advised courses of treatment.

To avoid developing emetine-resistance in the previously untreated, daily intravenous injections of 10 cgm. of emetine hydrochloride, in 1 per cent. solution, are being given without misadventure ; $\frac{1}{4}$ to $\frac{1}{2}$ mgm. of atropine concurrently will lessen the resultant immediate nausea. Emetine hydrochloride can also be given orally in gelatin capsules in doses of 4 cgm. thrice daily ; the drug is thus liberated for local action in the ileum or caecum, but unfortunately it causes emesis and is not well tolerated ; the same applies to E.B.I., and other preparations of emetine given orally. [The doses of emetine given above appear to be somewhat high.]

Conessine and the other alkaloids of *Holarrhena dysenteriae*, or of *H. floribunda*, exert an action comparable with that of emetine when used during dysenteric exacerbations, and provide an alternative to emetine. But these drugs, so readily given by mouth, are nerve excitants and may cause severe neuro-psychiatric disorder, especially in those with a predisposition in this respect. Their use should be confined to carefully selected cases treated in hospital. Conessine may be given concurrently with emetine, each drug reinforcing the action of the other ; alternatively it may be kept for use in cases found to be refractory to emetine.

The earlier iodo-oxyquinoline derivatives, such as chiniofon, to-day tend to be replaced by newer drugs of the diodoquin type. Treatment with these must continue over at least 20 days, and preferably over a month or more ; the action of these drugs is a local one on the parasites within the lumen of the bowel. Undue claims were initially made for diodoquin ; in view of its high iodine content (64 per cent.) it may raise the iodine blood-level. Newer iodine preparations now under test show promise, but it is too early to arrive at a true estimate of their value. It is sometimes advantageous to give such drugs concurrently with emetine. Aureomycin has now been tried and favourable reports received, especially in America, of its value in chronic cases.

The potential pathogenicity of strains of *E. histolytica* is a much debated subject : it is generally thought that some bacterial infection of the colon precipitates invasion of the gut wall by amoebae ; modification of the bacterial content of the colon of itself may suffice to do so by causing physico-chemical changes. The prevalent flora of the colon in the tropics differ from those in temperate climates, and this fact may explain the differences in pathogenicity of *E. histolytica* in these regions. The sulphonamides and penicillin have been used effectively in the treatment of chronic amoebic colitis when given concurrently with emetine treatment. The bacterial flora, by their fermentative activities within the colon, are responsible for the formation of indol, skatol and mercaptan, and they also synthesize a number of substances, in particular vitamins needed for nutrition and haemopoiesis. The antibacterial drugs affect especially the pyogenic organisms ; but the presence of these is not essential to the welfare of the amoebae, it is rather the proteolytic bacteria which facilitate amoebic invasion of tissue ; Moreover, it would now seem that bacteria are not indispensable to amoebae even in culture, the addition of pulped tissues to the medium provides the conditions necessary for their development in the absence of organisms. It thus seems that there are several factors which may cause the physico-chemical changes in the colon which promote tissue destruction by amoebae, and of these bacterial action is but one.

Turning to the second of the two clinical syndromes, the author states that this is encountered, in metropolitan France, as a sequel particularly of the

severe type of amoebic dysentery contracted in the Far East. The manifestations are varied and numerous; as they are not directly ascribable to a current amoebic invasion of tissue the parenteral administration of drugs such as emetine does not relieve them. Diagnosis of this syndrome presents difficulties, among which is the frequently prolonged absence of cysts from the stools. Treatment can be subdivided into three categories: (1) for the colitis, with the iodo-oxyquinoline drugs and with arsenicals; (2) for the eradication of the intestinal parasitic infection, which entails the use of conessine in addition to the drugs already mentioned; and (3) for clinical complications, such as exacerbations of diarrhoea, mental depression, etc., which are treated palliatively.

Some degree of "amoebic hepatitis" (without the presence of amoebae in the liver) is always evident in amoebiasis; it is ascribable to associated toxic and infective processes associated with the infection. This hepatitis responds readily to treatment with emetine or with conessine, and it subsides under the treatment advocated for the colitis. In true liver abscess emetine fails when there is an accompanying pyogenic infection and penicillin and a sulphonamide have been advocated in such cases, but surgical drainage is also usually necessary.

The author concludes with a résumé of the schemes of treatment he advocates under various conditions, and the particular drugs he employs.

A. R. D. Adams

HARINASUTA, C. **Chloroquine in the Treatment of Amoebic Liver Abscess.** *Indian Med. Gaz.* 1950, Feb., v. 85, No. 2, 37–41. 3 charts & 8 figs. on 4 pls.

Thirty-two cases of intestinal amoebiasis, 21 of amoebic hepatitis, and two of amoebic liver abscess have so far been recorded in the literature as responding satisfactorily to chloroquine treatment. Hepatic amoebiasis is common in Siam, where the author has treated nine cases of amoebic liver abscess with chloroquine; these are the subject of the present report. The dosage advocated has been 0·6 gm. of the base daily by mouth for 2 days, and then 0·3 gm. daily for 12 to 19 days; the author adhered to this dosage in all but the very severe cases; in these he continued the initial larger doses until a response was assured.

In all his cases there was alleviation of symptoms and signs within a few days, but two patients developed complications. The first of these after apparent cure was discharged from hospital, but 15 days later developed a cough with blood-stained sputum. On re-admission to hospital he was found to be febrile and expectorating anchovy-sauce material; there was a raised right diaphragm, and consolidation of the base of the right lung. Both a liver and a lung abscess were defined by the injection of opaque material. He was retreated with chloroquine with immediate improvement. The abscesses had largely resolved within 3 weeks.

The second patient had an amoebic abscess of the left lobe of the liver, and on the second day of treatment with chloroquine coughed up chocolate-coloured sputum. Another abscess was then found in the right lobe of the liver; this had penetrated to the right lung, the base of which showed consolidation. A daily dose of 0·6 gm. of chloroquine base was continued in this case; on the fifth day the blood pressure fell during the day from 104/74 to 78/52; on the sixth day it was 72/52. This fall was thought to be due to the drug and so it was stopped; the total dosage up to this time was 3·315 gm. Two days later, the blood pressure having risen to 92/64, chloroquine treatment was resumed at the rate of 0·3 gm. of the base daily, and was continued for another 14 days, the patient making an uninterrupted recovery.

In yet another case of the 9 a fall in systolic blood pressure from 98 to 80 was noticed on the third day of treatment, which was not discontinued, and the blood pressure subsequently returned to normal. In five of the remaining cases reductions of 10 to 18 mm. in the systolic blood pressures were observed during treatment with chloroquine, but the pulse rates did not markedly change during the hypotensive period and there were no subjective symptoms. A fall in blood pressure is a previously unrecorded effect of chloroquine, and is probably a toxic manifestation due to vascular dilatation. X-ray and clinical photographs illustrate two cases which are described in detail.

A. R. D. Adams

CONAN, N. J., JR., HEAD, J. A. & BREWER, A. E. **Pleural and Hepatic Amoebiasis treated with Chloroquine. Report of Two Cases.** *Trans. Roy. Soc. Trop. Med. & Hyg.* 1950, May, v. 43, No. 6, 659–66, 14 figs. (12 on 4 pls.) [18 refs.]

Chloroquine diphosphate has been reported to cure amoebic infection of the liver whether in the form of acute hepatitis, of an undrained abscess, or of an abscess draining pus containing parasites [numerous references are cited]. Some of these reported cases had already been unsuccessfully treated with emetine. Though chloroquine is effective in hepatic amoebiasis it is inferior to the usual amoebicidal drugs in the treatment of intestinal amoebiasis. The treatment by chloroquine of two cases of considerable amoebic infection of the pleura, a result of extension from amoebic liver infection, is now reported. In each of these cases the drug proved as effective as in those with purely hepatic lesions.

The first patient was admitted to hospital with an acute abdominal condition ; laparotomy revealed a ruptured amoebic liver abscess, and a second though unruptured abscess which was drained at the operation. A week later there was gross involvement of the right pleura, from which "anchovy sauce" material was aspirated. The dosage of chloroquine given in this case was 0·6 gm. of the base by mouth daily for 2 days, followed by 0·3 gm. daily for another 14 days ; "Milibis" (para-N-glycolyl arsanilate), an intestinal amoebicide, was given concurrently.

The second patient had suffered several attacks of liver disorder before amoebiasis was suspected to be the cause. A ten-day course of emetine with carbarsone was then given, but before the completion of this treatment the temperature rose abruptly and there was evidence of a right-sided pleural effusion. The liver was found to be still enlarged and tender, *E. histolytica* was still present in the stools, and an aspiration of the chest yielded a cloudy yellow fluid ; chloroquine treatment was then given orally at a dosage of 0·6 gm. of the base daily for 2 days, and then 0·3 gm. daily for 31 days. The symptoms abated and the signs largely vanished by the end of one week. "Milibis," 0·75 gm. daily for 7 days, failed to free the stools of parasites, but the substitution for this of diodoquin led to their disappearance.

Specimens of plasma and of liver were obtained at laparotomy from a volunteer after a loading course of treatment with chloroquine. These specimens were taken at about the time chloroquine had been observed to produce its clinical effect in cases of hepatic amoebiasis, that is 12 hours after the second dose of 0·3 gm. of the base (given once daily after 0·6 gm. daily for 2 days). The concentration of the drug found in the plasma of the volunteer was 0·180 mgm. per litre, and that in the liver 300·0 mgm. per kgm., a differential of 1,500 times. This plasma level approximates to the average plasma level in persons on a maintenance dosage of 0·3 gm. of the base, which is 0·176 mgm. per litre. The concentration of the drug in the liver is within the range of chloroquine concentration (1/3500 to +1/35000) shown to be amoebicidal *in vitro*.

The concentrations of chloroquine in plasma and in extracellular fluid should have no significance because of the 55 per cent. protein binding of the drug, but those achieved in the intestinal wall or lumen of the gut would be intermediate and at times significant.

"The pleural cavity and lung are, next to the liver, the commonest sites of extraintestinal amoebiasis. If the above hypothesis is correct, chloroquine should be active in pulmonary amoebic infections because it is localized in this tissue to the same extent as it is in the liver. While it is true that its concentration in pleural transudate would be lower than in the plasma, in pleural exudate, on the other hand, its concentration would be immensely increased by virtue of its high concentration in leucocytes which, as measured in blood, is 200 times the plasma concentration, and in purulent fluid would be even greater because of the greater number of leucocytes per ml. in such fluid as compared to blood."

X-ray photographs and detailed accounts of the two cases of amoebic pleural invasion are given in the text. *A. R. D. Adams*

LEUSCH. Rapport sur les essais thérapeutiques pratiques à l'aide de la Conessine (Roquessine). **Therapeutic Trials with Conessine.** *Ann. Soc. Belge de Méd. Trop.* 1950, Mar. 31, v. 30, No. 1, 113–17.

At the Hôpital des Noirs, Leo-Est, Belgian Congo, 10 Congolese patients were treated with conessine hydrochloride to a total dosage of 6 gm. as follows :—

5×0·1 gm. for 5 days.
4×0·1 gm. for 5 days.
3×0·1 gm. for 5 days.

There were no signs of intolerance, but "secondary effects" appeared in one case in the form of complete insomnia with tremors, and in another case of partial insomnia. This insomnia yielded to phenobarbitone. The dysenteric symptoms of those treated were relieved within three days ; only one patient of the 10 treated was passing parasites in the stools at the end of the treatment ; he was then treated with emetine ; shortly afterwards he developed an attack of paratyphoid fever.

Trials of an extract of the total alkaloids of *Holarrhena* were abandoned as this caused functional and organic evidence of toxicity ; emetine had to be substituted for it. *A. R. D. Adams*

SOULAGE, J. & PORTE, L. A propos de deux observations d'hépatites amibiennes traitées par le chlorhydrate de conessine. **Two Cases of Amoebic Hepatitis treated with Conessine Hydrochloride.** *Méd. Trop.* Marseilles. 1950, Mar.–Apr., v. 10, No. 2, 287–90, 2 charts.

PORTE, L. Bromhydrate de conessine. **Conessine Hydrobromide.** *Méd. Trop.* Marseilles. 1950, Jan.–Feb., v. 10, No. 1, 116–27, 3 charts.

Twenty-four patients (22 adults and 2 children) suffering from various manifestations of amoebiasis (including 9 considered to be due to "pre-suppurative amoebic hepatitis) were treated with conessine hydrobromide.

For adults weighing 65 kgm. the dosage was 0·5 gm. daily by mouth for 4 or 5 days, then 0·3 gm. daily to a total equivalent in grammes to about a tenth of the body weight in kgm. (4·5 to 5 gm. for persons of average weight). The clinical response was rapid ; parasites vanished from the stools by the 4th or 5th day at latest, but recurred about the 8th day for a greater or lesser period. There was no evidence of intolerance of the drug, but some patients complained of a bitter-tasting saliva. The pre-suppurative hepatitis cleared up

in a spectacular manner ; one patient with constipation and meteorism was speedily relieved of these symptoms. Toxic manifestations though distinctly less frequent and less marked than those associated with the hydrochloride were of a similar type ; the drug had to be stopped before completion of treatment in only one case, a young man suffering from latent tetany.

For children [one aged 3 years] the dosage was a total of 2 gm. for a body weight of 21 kgm ; the drug was well tolerated and the therapeutic result good.

The records of 9 cases are set out in detail. *A. R. D. Adams*

ARMSTRONG, T. G., WILMOT, A. J. & ELSDON-DEW, R. **Aureomycin and Amoebic Dysentery.** *Lancet.* 1950, July 1, 10–12.

Preliminary work by ANDERSON & ANDERSON [this *Bulletin*, 1950, v. 47, 749] and by BRADIN & HANSEN [*ibid.*, 538] suggested that aureomycin is not directly amoebicidal, but that it acts indirectly by destroying bacteria necessary to the life of the protozoan [but see also JONES, this *Bulletin*, 1950, v. 47, 748]. The results with aureomycin recorded here are based upon a series of fifty-two African cases of amoebic dysentery, five African cases of exceptional severity and four milder European cases. In Durban and its environs amoebic dysentery is endemic among the many thousands of Africans living in over-crowded quarters without any form of sanitation. Some 2,500 cases are admitted to King Edward VIII Hospital yearly. Only males and those passing blood and mucus with ulcerations seen by sigmoidoscopy were studied in this series. Cyst-passers were not accepted.

Sigmoidoscopy was performed daily till all ulcers had healed and whenever possible scrapings were examined microscopically.

Follow-up after treatment was unfortunately incomplete.

Aureomycin was given by the mouth in doses of 0·25 gm. four times daily at intervals of 6 hours for 15 days. No other active drug was given. Daily sigmoidoscopy revealed a remarkably rapid rate of healing. Twelve patients were completely healed by the 4th day and at the end of 7 days no less than twenty-nine were healed.

Healing began at the periphery of the ulcers, but sometimes the whole surface of the ulcer acquired epithelium simultaneously in a matter of a few days.

Clinical improvement preceded healing by several days, and diarrhoea ceased usually after 1–2 days.

Disappearance of amoebae was likewise rapid and dramatic. By the 4th day, 37 out of 51 cases had been cleared of these parasites. By the 9th day all were free, except one who failed to respond throughout.

A remarkable feature observed was the great increase in size of the amoebae on the 3rd and 4th days when they reached a length of 90 μ in some cases.

Relapse rate was high in spite of the remarkable immediate results. One month after discharge twenty-seven of the successful patients returned, but twenty were well, free of amoebae, and without ulceration at sigmoidoscopy. One died suddenly from fulminating amoebiasis and clinical diphtheria.

Three relapses occurred within 2 weeks of discharge : two within 3 weeks, and two at 4 weeks. One patient had hepatitis. All ultimately responded to emetine and diodoquin.

Out of five severe African cases three patients were found at sigmoidoscopy to have very large ulcers covered with thick tenacious sloughs. Two were dehydrated, necessitating treatment by intravenous drip. One of these was free of amoebae on the 3rd day, another on the 5th and the third on the 7th. In one, all ulcers were healed on the 17th day and follow-up a month after discharge showed the patient to be well and free from ulceration of the colon.

The second patient, on the other hand, had unhealed ulcers on the 20th day and was given emetine and diodoquin with success on the 34th day. The third showed only slight improvement, though with combined emetine he made a slow recovery.

In a fourth patient the rectum was severely involved and covered with a tenacious greenish-black and grey slough which was later passed as a necrotic slough, but with aureomycin treatment a clean granular surface was left in which a stricture subsequently developed. Emetine and diodoquin subsequently completed the cure.

In four Europeans the drug was apparently more successful. These included a baby of 10 months who was successfully cleared of trophozoites.

Comparisons were made with other drugs, alone and in combination. The results are shown in a table. The list includes emetine alone ; diodoquin alone ; emetine and diodoquin ; diodoquin and emetine ; bismuth iodide ; penicillin and sulphasuxidine followed by emetine and diodoquin ; penicillin, sulphasuxidine, emetine and diodoquin ; sulphasuxadine, emetine and diodoquin ; penicillin and sulphasuxidine ; sulphasuxidine for 20 days ; penicillin alone for 20 days ; phthalyl sulphacetamide alone ; carbarsone alone ; emetine-bismuth iodide alone ; aureomycin alone. The results show that aureomycin is capable of producing a very high cure rate at 20 days. Successes with emetine are assessed at 50 per cent., with aureomycin at 94 per cent.

Unfortunately the relapse rate is high and is probably higher than with the other drugs, and suggests that aureomycin should not be used alone, but should be combined with one of the hitherto accepted amoebicides : when combined with aureomycin, the dosage of emetine or emetine-bismuth iodide could probably be drastically reduced. [See also this *Bulletin*, 1950, v. 47, 746-9.]

P. Manson-Bahr

RELAPSING FEVER AND OTHER SPIROCHAETOSES

BALTAZARD, M., MOFIDI, C., BAHMANYAR, M., SEYDIAN, B. & HABIBI, A. Sur la transmissibilité des spirochètes récurrents par le pou. [**On the Transmissibility of Relapsing Fever Spirochaetes by the Louse.**] *Bull. Soc. Path. Exot.* 1950, v. 43, Nos. 3/4, 176–86, 1 chart. [11 refs.]

The authors have continued their experiments on the possibility of transmitting relapsing fever spirochaetes by means of human lice. In all cases the lice were fed on newly born rabbits containing spirochaetes in the blood, then fed for a number of days on human subjects, and subsequently ground up and examined under the dark field ; finally the emulsion was inoculated into susceptible animals such as newly born rabbits or rats.

Spirochaeta parkeri produced a severe infection in newly born rabbits. Three experiments on its transmission by lice were all positive.

Spirochaeta gallinarum, although a specific infection of birds in nature, transmitted only by *Argas*, was found under experimental conditions to be capable of transmission by lice. Three experiments were made in which the lice were fed on infected chicks, and another three in which newly born rabbits infected with the spirochaete were used, and in all cases the results were positive.

The authors summarize the results of transmission experiments with lice, dividing the spirochaetes into three groups :—

(1) Spirochaetes non-pathogenic to guineapigs and adult rabbits :—

S. duttoni, microti, turicatae, hermsi, merionesi, crocidurae, parkeri, novyi have all given positive results. *S. normandi*, in one experiment, gave negative results.

(2) Spirochaetes pathogenic to guineapigs and adult rabbits :—

S. hispanica, positive. *S. persica* has given uniformly negative results.

(3) Spirochaetes non-pathogenic to mammals :—

S. gallinarum, five positive results out of six experiments.

These results show that a wide range of relapsing fever spirochaetes are able to persist in the louse, which under favourable conditions may occasionally become the carrier of infections not naturally occurring in man. In this way there is a possibility of new human infections arising from other mammalian hosts. *E. Hindle*

PFISTER, R. Contribution à l'étude des spirochétolysines dans les fièvres récurrentes à tiques. [**A Contribution to the Study of Spirochaetolysins in Tick Relapsing Fever.**] *Méd. Trop.* Marseilles. 1949, Nov.–Dec., v. 9, No. 6, 985–90. [19 refs.]

The author has examined the sera of 15 guineapigs for lysins after periods ranging from 2 days to 10 months after recovery from infection with *Spirochaeta hispanica*. The results were uniformly negative concerning the presence of spirochaetolysins, no difference ever being observed between spirochaetes exposed to the action of serum from normal guineapigs or from animals that had recovered from the infection. [See also this *Bulletin*, 1949, v. 46, 837.] *E. Hindle*

NÉEL, R. & PAYET, M. Fièvre récurrente à tiques de Madagascar. Sensibilité des animaux de laboratoire. [**Madagascar Tick Relapsing Fever. The Susceptibility of Laboratory Animals.**] *Bull. Soc. Path. Exot.* 1950, v. 43, Nos. 3/4, 186–95. [10 refs.]

The authors have studied three strains of this little-known spirochaete, two isolated at Tananarive but from patients coming from Soalala, and the third from a patient from Mitsinjo. In all cases the strains were obtained by inoculating white mice with blood from the patients. Slight differences were observed in the virulence of the three strains in mice and rats. In mice a blood infection was produced without any mortality. Residual brain infections were also developed, in one case being observed after 157 days.

Rats were also susceptible, but the duration and intensity of the blood infection was much less than in the mouse. There was no mortality and residual brain infections developed.

Guineapigs were completely non-susceptible.

A few experiments with newly born mice, rats and guineapigs, emphasized differences between the strains. Also the newly born guineapig showed a short infection sometimes followed by a longer inapparent infection during which its blood was infective. The newly born rat was found to be more susceptible than the newly born mouse, unlike the behaviour of the infection in the adults.

In its general characters the spirochaete of Madagascar tick fever resembles *S. duttoni*, but seems less pathogenic to mice and rats. *E. Hindle*

YEO, R. M. **Tick-borne Relapsing Fever on the Witwatersrand Gold Mines. Its Treatment with Aureomycin.** *South African Med. J.* 1950, June 17, v. 24, No. 24, 457–9.

The Witwatersrand Native Labour Association examines approximately 300,000 African labourers yearly on their way to or from the Witwatersrand. Of these approximately a third are recruited outside the Union of South Africa, and many tropical diseases are met with which do not occur to any great extent in the South African Bantu.

Tick-borne relapsing fever occurs only sporadically in the Union, but is common in Northern Rhodesia. By the time the labourer reaches Johannesburg the disease has usually reached a chronic stage and in only a small percentage of cases are the acute symptoms seen and a detailed description of these need not be given. The average duration of pyrexia is from 12 to 72 hours. Of a series of 100 cases, 5 had six relapses before leaving hospital and one had eight before being repatriated. The diagnosis of all cases was made by examination of thin or thick blood films taken during the pyrexial period and stained with Leishman's or Giemsa's stain, the spirochaetes being often scanty and requiring a long search [*cf.* the disease in East Africa where the organism is usually quickly found in infected Africans]. In addition confirmation of the diagnosis has been made in many cases by a complement fixation test, with the use of a suspension of *Sp. duttoni* prepared from egg cultures of the organism. In 100 cases treated with arsenicals, penicillin, sulphonamides, anthiomaline and anti-protozoal drugs, or untreated, 70·5 per cent. had one or more relapses.

Twenty-five patients were treated with aureomycin orally and only three had a relapse. One patient not included in the series relapsed after receiving 3·0 grammes during an apyrexial period.

Among the earlier cases experiments were made with a commencing dose of 2·0 gm., followed by 0·25 gm. every four hours while the pyrexia lasted. Two patients receiving this initial dose complained of nausea and vomiting and one showed a marked pyrexia within 24 hours of the administration of the drug. It was decided to give an initial dosage of 0·5 gm. followed by 0·25 gm. every four hours until the temperature had been normal for 12 hours. No other treatment was given at the time and the average total given per case was 3·0 gm. The pyrexia which was about 103°F. at the commencement of the attack fell rapidly by crisis, accompanied by profuse sweating, and was usually normal within 24 hours. With the fall in temperature there was a rapid improvement in symptoms. One case, a severe one with iritis and jaundice, relapsed in 24 days after having received 3·5 gm., one relapsed 15 days after 1·5 gm. of aureomycin but had no further relapse after a second course of 3·0 gm. One relapsed 12 days after receiving only a single dose of 1·0 gm.

After treatment with this drug there is a rapid diminution in the size of the spleen and in most cases it is no longer palpable three weeks after completion of treatment. Of the remaining cases there were no relapses within three weeks of treatment. There was an average gain in weight of 6·1 lb. after the last relapse. All patients were given an iron tonic together with a vitamin and protein mixture [presumably after completion of aureomycin treatment].

It is thought that a more concentrated course of treatment with a larger dosage would eliminate the spirochaete altogether from the body, and experiments are now being carried out on these lines. The effect of aureomycin on the complement fixation titre has not yet been observed. *C. F. Shelton*

YAWS

LE GAC, P. J. & MULLET. Goundou bilatéral des os malaires observé chez un indigène de l'Oubangui (A.E.F.). [**Bilateral Goundou of the Malar Bones in a Native of Oubangui (French Equatorial Africa).**] *Méd. Trop.* Marseilles. 1950, Mar.–Apr., v. 10, No. 2, 325–6, 1 fig.

This case refers to an African aged 30 who had two ovoid symmetrically situated masses on the face, each at the level of the cheek bone. They proved on clinical examination to be bony protuberances associated with the malar bones: no evidence of osteitis was found elsewhere. The patient gave a history of yaws in childhood. No X-ray pictures were taken.

The interest of this case lies in the rarity of the localization. The authors quote BOTREAU-ROUSSEL [this *Bulletin*, 1925, v. 22, 421] who found only one case of goundou affecting the malar bones among 249 cases of bone lesions due to yaws seen on the Ivory Coast. The case is clearly illustrated by a photograph. *H. J. O'D. Burke-Gaffney*

BOTREAU-ROUSSEL. Le pian en Indochine. [**Yaws in Indo-China.**] *Rev. Méd. Française d'Extrême-Orient.* 1941, July–Aug., v. 19, No. 7, 615–28, 8 figs.

BOTREAU-ROUSSEL, RIBO & SUA, H. B. Deux cas de goundou en Indochine. [**Two Cases of Goundou in Indo-China.**] *Rev. Méd. Française d'Extrême-Orient.* 1941, July–Aug., v. 19, No. 7, 629–30, 2 figs.

FERREIRA, F. C. & PINTO, A. R. Le traitement du pian par un dérivé de l'acétarsone. [**Treatment of Yaws with an Acetarsol Derivative.**] *Bull. Soc. Path. Exot.* 1950, v. 43, Nos. 1/2, 33–7.

This is a report of the treatment of 35 cases of primary and secondary yaws in Portuguese Guinea with Friedheim's S.T.B. (a trivalent derivative of acetarsol, namely 4-oxy-3-acetylaminophenylarsenoxide) in 5 consecutive daily doses by mouth of 0·01 gm. per kgm. body weight. Curative effects were rapid and the day after the completion of treatment "60 per cent." of patients were healed. A month after treatment 31 were healed and 2 had relapsed. After three months all were healed and the 2 relapses had responded to acetarsol. This supports the earlier report by FRIEDHEIM [this *Bulletin*, 1949, v. 46, 839]. No signs of intolerance were observed. No serological data are given.

C. J. Hackett

LEPROSY

CHAUSSINAND, R. L'expansion de la lèpre à travers le monde. [**The Spread of Leprosy throughout the World.**] *Rev. Méd. Française d'Extrême-Orient.* 1943, Aug.–Sept.–Oct., v. 21, Nos. 7/8, 618–26. [10 refs.]

CHAUSSINAND, R. Revue statistique de 641 cas de lèpre observés de septembre 1940 à juin 1942 au dispensaire antilépreux de l'Institut Pasteur de Saigon. [**Statistical Study of 641 Cases of Leprosy seen between 1940 and 1942 at the Leprosy Dispensary of the Pasteur Institute in Saigon.**] *Rev. Méd. Française d'Extrême-Orient.* 1942, Aug.–Sept., v. 20, No. 7, 910–25.

CAMUS GUNDIÁN, D. La Lepra en la Isla de Pascua. [**Leprosy in the Isla de Pascua.**] *Rev. Med. Chile.* 1950, Feb., v. 78, No. 2, 135–40.

This area was visited by a Commission which included 8 doctors to study medical problems there in October 1947. At that time the total population

was 720, made up of 685 " natives ", mostly Polynesians of Maori descent, 30 Chilenas and 5 " foreigners ". Among these, 51 leprosy patients were seen, 28 males, 23 females ; 12 (6 of each sex) between 6 and 14 years of age, 18 (10 males, 8 females) between 15 and 20 years ; 13 (9 and 4) between 21 and 30 years, 4 (two each) between 31 and 40, and 4 (3 and 1) over 40 years. Of these, 18 were in leprosaria, 9 of them (6 males, 3 females) in one for long-standing cases, and 9 (1 and 8) in one for early cases ; 22 were ambulatory, 14 males, 8 females, 8 of whom (6 and 2 respectively) were classed as contagious and 7 had Hansen's bacilli in the nasal mucus ; another 11 were " under control ", but this means little. They showed no active lesions, were in good general health and went about freely, the control being " periodic ".

The plan of campaign against the disease comprises segregation in a leprosarium of active infective patients ; erection of a new leprosarium with separate quarters, provision of nurses and others to attend on the patients, modern forms of treatment, etc. There is a Society known as " Friends of the Isle of Pascua " which does good work among the community.

H. Harold Scott

Do Páteo, J. D., Jr. Da lepra incipiente na vigilancia sanitária dos fócos domiciliares. (Estudo dos communicantes.) [**Early Signs of Leprosy among Home Contacts.**] *Rev. Brasileira Leprologia.* S. Paulo. 1949, Dec., v. 17, No. 4, 249–63, 4 graphs.

Even with a careful watch being kept on contacts of leprosy patients it is far from easy to determine exactly when actual signs of infection appear. The patient may not himself know and the medical practitioner from sheer lack of knowledge of the disease may overlook early signs. The author has endeavoured to keep under his observation, by half-yearly examinations for 5 years, over 72,000 contacts since 1945 and among them 796 have developed the disease. " Five years " was chosen because that is regarded as the average incubation period of the disease. In that time those up to 5 years of age totalled 665 or 83·5 per cent. of the whole [the letterpress states 601 cases or 75·05 per cent., but a tabular record gives 64 under one year, 379 from one to three years, and 222 from three to five years, which total 665. In a summary of the table the same mistake is made.] Of the 796 there were 414 males (52 per cent.) and 382 females (48 per cent.). Ninety-six (12 per cent.) were of the lepromatous type, 639 (80·2) indeterminate and 61 (7·6) tuberculoid. The number of indeterminate seems unduly high, but it must be remembered that early signs were being looked for and some, perhaps many, of these will later take on the characters of one or other of the more definite types. The examination showed that the young were particularly susceptible. The figures up to 5 years have been given ; another 128 (16 per cent.) were between 5 and 10 years, 3 were between 10 and 15 years and after that age the likelihood [the author uses the word " *possibilidade* "] of contagion decreases sensibly.

A series of tables sets forth these and other facts and the author concludes that periodic examination is the most practicable and the safest means of determining the age at which symptoms and signs of leprosy arise among contacts ; that females show a greater resistance to infection [but the difference is not very great, 48 and 52 per cent. for females and males respectively] and are more often of the tuberculoid type ; lastly, there is a strict relation between the appearance of lesions and the sexual development.

H. Harold Scott

URRETS ZAVALIA, A. Resultados del examen gonioscopico de los enfermos de lepra. [**Gonioscopy in Leprosy Patients.**] *Rev. Brasileira Leprologia.* S. Paulo. 1949, Dec., v. 17, No. 4, 227–36. [12 refs.]

Gonioscopy, or examination of the angles of the anterior chamber of the eye, was performed on 29 leprosy patients. Ten were suffering from the tuberculoid form, two from the non-characteristic, and two had been of the latter type but had recently become transformed into the lepromatous. In these 14 no changes were observed, but in the 15 which had been for a long period exhibiting symptoms of the lepromatous form there were visible lesions of the iris and at the junction of the iris and the cornea, like those described by PUIG SOLANES in onchocerciasis [see this *Bulletin*, 1950, v. 47, 483]. These lesions comprised miliary nodules and synechiae, with loss of substance at the base of the iris. Brief notes of 15 cases are given. In one, miliary nodules were seen in an eye to all appearances free from leprous lesions, but in the other eye leprosy lesions were present in the cornea and iris. *H. Harold Scott*

ROSS, Hilary & GEMAR, F. **Comparative Studies of the Cardiolipin Antigens with the Regular Antigens in the Kolmer Complement Fixation and the Kahn Precipitation Tests in Leprosy.** *Internat. J. Leprosy.* 1949, Oct.–Dec., v. 17, No. 4, 383–8. [18 refs.]

This report concerns the findings when cardiolipin antigen was used in the Kolmer and Kahn tests on sera from leprosy patients in Carville. In the V.D.R. Laboratory in 37 cases the Kolmer test gave 20 positives with cardiolipin as against 6 with standard antigen : in 39 other cases the corresponding figures for the Kahn test were 16 and 22. In the case of 260 sera from cases of leprosy tested by various routine methods 111 had been positive with the Mazzini, 169 positive with the Kolmer and 214 positive with the Kahn and 35 had been negative with all tests. In the present study the 225 sera which had given positive results were tested in parallel by the Kolmer and Kahn reactions with the use of standard and cardiolipin antigens. The Kolmer gave 101 positive reactions with standard antigen and 151 with cardiolipin ; the corresponding figures for the Kahn were 159 and 112.

The fact that the Kolmer and Kahn tests with standard antigen gave fewer positive reactions in the latter series is attributed to intensive sulphone treatment.

Thus it appears that the Kolmer reaction gives more false positive reactions in leprosy when cardiolipin antigen is used and the Kahn less ; [what may be the explanation is not clear]. *T. E. Osmond*

LOWE, J. **Dosage of Diamino-Diphenyl Sulphone.** [Correspondence.] *Lancet.* 1950, July 1, 36–7.

In this letter, Dr. Lowe refers to his previous papers on the treatment of leprosy with diamino-diphenyl sulphone (D.A.D.P.S.) by the mouth [this *Bulletin*, 1950, v. 47, 474, 475].

Previously he had suggested that a dosage rising to 300 mgm. daily by the fifth week, though well tolerated by Africans in Nigeria, might be unduly high. Later studies have now shown him that a lower dosage is effective and similar findings have been reported by MOLESWORTH and NARAYANASWAMI [*ibid.*, 474].

The author finds that a weekly dosage of 700 mgm. (100 mgm. daily for 7 days) usually suffices to produce a good clinical and bacteriological result, but he prefers to give more.

At present, he employs the following four systems :—

Dose (mgm.) and frequency	*Weekly total (gm.)*
(1) 300, six days a week	1·8
(2) 300, alternate days excluding Sundays ...	0·9
(3) 200, six days a week	1·2
(4) 500, twice a week	1·0

In lepromatous cases, there is so far no significant difference in the response to these differing dosages but in tuberculosis cases a more rapid response seems to be produced by daily administration. The lower dosage is rather more easily tolerated, though the higher has caused little trouble.

The author adds that three different workers in India have informed him that Indians appear to tolerate D.A.D.P.S. less readily than Africans and that the original recommended dose of 300 mgm. daily was too high for them. He therefore points out that, in the light of new experiences, the dosage can be reduced with little or no therapeutic loss and with a still further reduction in cost.

He stresses the vital necessity of a slow induction of treatment with D.A.D.P.S., even with the lower dosages ; the standard dose should not be reached for at least a month to six weeks, or perhaps even longer.

H. J. O'D. Burke-Gaffney

MAUZÉ, J. A propos du traitement de la maladie de Hansen par le dérivé 4,4 de la diaminodiphénylsulfone. [**Treatment of Leprosy with the 4,4 Derivative of Diaminodiphenylsulphone (Diasone).**] *Bull. Soc. Path. Exot.* 1950, v. 43, Nos. 5/6, 253–4.

The author, in Guadeloupe, was able to treat " a certain number " of patients in the leprosy settlement at Désirade with the 4,4 derivative of diaminodiphenylsulphone [diasone].

Owing to the isolation of the island records are incomplete, but a case is recorded of a man of 48, who had suffered from leprosy for at least 15 years. He had been treated with chaulmoogra oil for many years, which kept the condition stationary until 1945, when the patient recorded increasingly defective vision, amounting almost to total blindness. This was accompanied by a very painful rheumatoid syndrome affecting all the joints, which greatly hindered movement.

He was treated with " small doses " [unspecified] of diasone. Within 3 weeks, after 21 tablets, both his conditions improved and continued to do so under treatment. By the seventh week, he was reading without spectacles : from the fourth month onwards his improvement was maintained under treatment and the rheumatic pains coincided only with the increasingly rare appearance of lepromata. The reduction in red corpuscles was slight (from 3·7 to 3·2 million per cmm.). His improvement now persists after 2½ years.

It would have been of interest, as the author notes, to have had an ophthalmological examination to determine the exact lesion — presumably an iritis.

The author adds that he has seen some cases in which severe rheumatoid pains affecting the large joints occurred during the early stages of treatment with diasone : but these disappeared when treatment was ceased or reduced and strong doses of alkali were given.

[This recovery of sight after 2½ years of almost complete blindness is very encouraging.]

H. J. O'D. Burke-Gaffney

MUIR, E. & ROY, A. T. **Tar and Kerosene Paint for Tinea complicating Leprosy.** *Internat. J. Leprosy.* New Orleans. 1950, Jan.–Mar., v. 18, No. 1, 21–2, 4 figs. on pl.

DE SOUZA-ARAUJO, H. C. **Rat Leprosy : Susceptibility of the Black Mouse (American Race) to the Stefansky Bacillus. Preliminary Report.** *Internat. J. Leprosy.* New Orleans. 1950, Jan.–Mar., v. 18, No. 1, 49–52, 4 figs. on pl.

" The black mouse used, inoculated with Stefansky bacillus material, has developed typical lesions of rat leprosy in a very short time, showing itself to be more susceptible than any other animal used.

" From lesions induced in the black mice inoculated with such material, two cultures of acid-fast bacilli have been obtained."

HELMINTHIASIS

MENDHEIM, H. & SCHEID, G. Untersuchungen über den Wurmbefall in einigen Stadt- und Landkreisen Oberbayerns. [**Investigations of Worm Infection in some Town and Country Areas in Upper Bavaria.**] *Ztschr. f. Tropenmed. u. Parasit.* Stuttgart. 1950, Apr., v. 1, No. 4, 553–60, 2 charts. [15 refs.]

These studies ended in July, 1947. For faecal examinations the authors used the method of DE RIVAS and the saturated salt solution method of FÜLLEBORN, after trials of zinc sulphate and sodium nitrate as floatation fluids had failed to give better results. Floatation methods are indispensable for the detection of the eggs of the whipworm (*Trichuris trichiura*) and those of the dwarf tapeworm (*Hymenolepis nana*). Anal swabs for *Enterobius* were made by the Cellophane method of HALL. The investigations were done in the medical and children's clinics of the University of Munich and in Bad Reichenhall. Tables show the percentage incidence of *Ascaris lumbricoides, Trichuris, Taenia saginata* and *T. solium, Hymenolepis nana, Hymenolepis diminuta* and *Enterobius* (*Oxyuris*).

A total of 826 persons was examined. *Enterobius* was found in 62 per cent. of the children and in 44·3 per cent. of the adults. *Ascaris* was found in 14·1 per cent. of the children and 11·3 per cent. of the adults. *Trichuris* was found in 9 per cent. of the children and in 8·5 per cent. of the adults. Excluding *Enterobius*, *Ascaris* was the commonest worm found. More people infected with worms were found in Bad Reichenhall than in the Munich children's clinic. This agrees with the results obtained by other workers who have found *Ascaris* commoner in rural districts, but in general the incidence was less than in other areas of Germany. In Upper Bavaria the permeable soil which retains little moisture does not favour the development of *Ascaris* eggs and intensive garden cultivation characteristic of other parts of southern Germany is absent. A curve shows the rise of *Ascaris* infection in Bad Reichenhall since 1938, when the percentage incidence was 3·8. A second curve shows the variations of the infection during the year. A maximum in June is due to spring manuring and a rise in February to the autumn and winter manuring.

Taenia solium was found only once, *Taenia saginata* more often. *Hymenolepis nana* was found twice in children and *H. diminuta* (the rat species) once. In the same area 85 patients were treated for tapeworms by the authors.

Table 3 shows the results of single anal swabs taken to detect *Enterobius*, and this would not detect all the infections. By repetition of the examinations one would expect an increase of the incidence by about one-third. Adults were less often infected than children, but females were more often infected

than males. Infections of healthy and sick children were not different. Out of 212 adults studied by stool examination and anal swabs in the Munich clinic, 58·9 had worm eggs, and of these 44·3 per cent. had *Enterobius*, 11·3 per cent. *Ascaris*, 8·5 per cent. *Trichuris* and 4·2 per cent. *Taenia* spp. Stool examination and anal swabs done on 234 children in the Munich clinic showed that 72·8 per cent. had worm infections and that *Enterobius* was present in 62 per cent., *Ascaris* in 14·1 per cent., *Trichuris* in 9 per cent. and *Taenia* spp. in 1·3 per cent. A table shows the age incidence in these children also. *Enterobius* infection increased at the beginning of the school term. The heaviest infections with *Ascaris* and *Trichuris* occurred between the ages of 4 to 6.

In 20 of 212 adults examined at the Munich clinic infections with more than one species of worm were found. *Enterobius* and *Trichuris* were found in 9, *Enterobius* and *Ascaris* in 6. All those harbouring *Taenia* also had *Enterobius*.

In the rural area *Ascaris* and *Trichuris* were commoner, in the town area *Enterobius* was more frequent. Family infections were often found. Worm infections have increased since the last war. The authors suggest that the increase of *Enterobius* is due to lack of soap and washing and to better methods of diagnosis and among children to restriction of school space. Increase of *Ascaris* is related to lack of sanitation in rural areas and intensive manuring with human faeces, though this is less evident in the more gravelly soil of Upper Bavaria where there is less intensive cultivation. The authors found in Munich and the other areas of Upper Bavaria an increase of *Ascaris* infections to twice or three times that shown by earlier studies. They did not find that the incidence of *Trichuris* had increased. *D. latum* was not found.

G. Lapage

DE AZEVEDO, J. F., COELHO, M. F. & DE CARVALHO, F. As parasitoses intestinais nas crianças de alguns asilos de Lisboa. [**Intestinal Parasites in Inmates of Children's Homes in Lisbon.**] *Anais Inst. Med. Trop.* Lisbon. 1949, Dec., v. 6, 47–64, 1 fig. [25 refs.] English summary.

The authors studied the incidence of intestinal parasites in 334 children aged 7 to 14 in certain children's homes in Lisbon. Specimens of faeces were examined by direct smear and by Willis flotation method and, where eggs of *Enterobius* were being searched for, by the N.I.H. swab. Detailed results are shown in 5 tables. It is stated that 95·2 per cent. harboured pathogenic parasites. These included 90·4 per cent. of *Enterobius*, 46·22 per cent. of *Trichuris*, 8·43 per cent. of *Ascaris* and 7·2 per cent. of *Hymenolepis*. There were also 5·52 per cent. of ankylostomes, but the infected children had come from Portuguese colonies.

The percentages of protozoa were *Entamoeba coli* (18·77), *Giardia* (14·5), *I. bütschlii* (4·94) and *Chilomastix* (2·03). No mention is made of *E. histolytica* having been found. Most of the children (232) had more than one parasite and 95 of them had 3 to 5 parasites.

In a comparative study of methods for detecting *Enterobius*, it was found that only 0·2 per cent. were found by direct smear, 8·1 per cent. by Willis method and 90·4 per cent. by the N.I.H. swab when more than one examination was made. With a single examination by the N.I.H. technique, 77 per cent. of cases were detected.

The authors consider that *Ascaris* and *Trichuris* are commoner in North than in South Portugal, because of meteorological, topographical and agricultural factors (these are discussed and illustrated by a map). The incidence is greater in rural than in urban areas.

H. J. O'D. Burke-Gaffney

GONZÁLEZ CASTRO, J. Relaciones mutuas entre helmintos y microbios. Papel vectorial de los helmintos. [**Mutual Relations between Helminths and Microbial Bodies. Helminths as Vectors.**] *Rev. Ibérica de Parasit.* 1950, Apr., v. 10, No. 2, 205–73, 2 graphs. [Bibliography.]

This article covers a very wide field and contains sufficient material for a score of papers. In fact, in the opinion of the abstracter, one of its main advantages and values will be the stimulus it should give to many other researches. First, the antagonism between helminths and bacteria is discussed, an antagonism which appears to be reciprocal, bacteria attacking worms and worms devouring bacteria and passing them to the outer world; next, the reciprocal antagonism between moulds and helminths, and the action of helminths and their larvae in transmitting bacteria, moulds and viruses; lastly, the possible vector action of helminths with protozoa, for example, *Dientamoeba fragilis* and *Ascaris* or *Trichuris*, as suggested by Dobell ten years ago. *H. Harold Scott*

NÁJERA, L. Ein Verfahren für die Konzentration von Helmintheneiern in den Faeces. [**A Technique for the Concentration of Helminth Eggs in the Faeces.**] *Ztschr. f. Tropenmed. u. Parasit.* Stuttgart. 1950, Apr., v. 1, No. 4, 571–5, 5 figs.

The author uses a glass vessel, of which a drawing and a photograph are given; this has roughly the shape of a milk bottle without glass ends. The base of the vessel is 24 mm. wide and its total height is 62 mm. The two open ends are closed by cork or rubber stoppers. The faecal sample is put in at the lower, wider end together with some glass beads and this end is closed with the stopper. The vessel is then turned so that the narrower end is uppermost and saturated salt solution is poured into it till it is nearly full. The narrower end is then corked up and the vessel is shaken till a homogeneous faecal emulsion is obtained. The vessel is then put on the laboratory bench or in a Petri dish, broader end downwards. The narrower end is uncorked and enough saturated salt solution is added to bring the fluid to the upper margin of the narrower opening. This opening is then covered with a coverglass. After 20 to 30 minutes the eggs adhere to the underside of the coverglass, which is removed to a slide for examination. Theoretically the concentration of eggs obtained in this way is 25 times greater than that obtained with straight-sided vessels, but actually it is less, because the concentration is so great that some eggs adhere to the walls of the vessel and the depth of saturated salt solution is greater than in the vessels usually used. Even so the concentration of eggs is ten to 15 times greater. Additional advantages are: less smell in the laboratory, homogeneous faecal emulsion, greater rapidity of examination and easier identification of the eggs. There is one disadvantage. Air bubbles created by the shaking collect on the coverglass, but these can be broken up before the coverglass is put on, by putting three to four drops of amyl alcohol on the surface of the faecal emulsion. *G. Lapage*

PINTO, A. R. Os primeiros dados sobre a existência da schistosomíase vesical na Guiné Portuguesa e importância da contagem de ovos do parasita no sedimento urinário. [**Urinary Schistosomiasis in Portuguese Guinea; the Importance of Counting the Ova in the Urine.**] *Anais Inst. Med. Trop.* Lisbon. 1949, Dec., v. 6, 75–114, 29 figs. (24 on 7 pls.) & 1 map. [22 refs.] English summary.

This thesis gained the Tropical Medicine Award in 1949. The focus studied was about the Caiomete and Pelundo rivers, an area given up largely to rice

cultivation. The inhabitants of 15 villages were examined, the smallest, Bachegue, having a population of 90 and the largest, Bajope, 800, but the actual numbers examined were very small ; in five of the villages fewer than 20 were examined, in nine between 20 and 40, and in one only were 49 examined. The specimen of urine passed was examined after settling for half an hour ; if ova were not seen or were very few, the specimen was centrifuged. The totals examined (403), the numbers positive (218) and the percentages are given in a table and varied considerably within the small limits. Thus, of 16 examined in Bucucute (population 200), all were positive, whereas of 49 in Petabe (population 444) only one was positive. [The author's summary of these findings states : Total examined 502, number positive 265 and negative 237, but according to the detailed table the figures are as given above.] The incidence by sex and age as given is of no statistical value, because only two villages are considered and these have the smallest population, 90 and 160, and the numbers examined 20 and 31 respectively. Egg-counts were made on the same patients in the morning and in the afternoon, but only eight patients were so tested for eight consecutive days and out of the total of 128 examinations made, on only 11 occasions did the morning figure exceed that of the afternoon. " The mean value of the egg-counts [per slide] was directly proportional to the percentage of infected people ", says the author [but this is surely too great a claim to make on so few examinations].

The vector is *Pyrgophysa* [*Bulinus*] *forskali* ; another snail present is *Bulinus dautzembergi* ; no furcocercariae were found in either, but xiphidiocercariae were seen in the former.

The blood picture was studied in eight cases ; red cells ranged between 4,700,000 and 3,420,000 per cmm. and the haemoglobin between 52 and 72 per cent., so the anaemia was in no case severe ; leucocytes varied between 5,900 and 17,000, but most were between 6,000 and 8,400 ; eosinophilia was high, 21 to 33 per cent., but in these there was ankylostome infection as well as the schistosome.

Treatment by anthiomaline was given to eight children and at first proved unsatisfactory as eggs were still found ; but more prolonged treatment, with five additional injections, brought about a cure. *H. Harold Scott*

Colaço, A. T. F. O miracil D no tratamento da schistosomíase vesical. [**The Treatment of** *Schistosoma haematobium* **Infestation by Miracil D.**] *Anais Inst. Med. Trop.* Lisbon. 1949, Dec., v. 6, 149–63. English summary.

In the first part of this paper the author tells of the records which others have made on the treatment of urinary schistosomiasis with Miracil D. He then goes on to report his own experience in treating 15 patients in Algarve Province, Southern Portugal, with a total daily dose of 20 mgm. per kilo body-weight, divided into three doses and taken between meals. The full course should be of five days, but only three were able to complete it ; five bore it for four days, the others gave up after two or three days, complaining of insomnia, loss of appetite, feelings of fatigue and debility, tinnitus, headache, dizziness, nausea, vomiting and abdominal pain. Of those who were able to take the drug for four days, " 60 per cent. were cured " [? three of the five ; or, if those who tolerated the drug for five days are included, the number would be " 60 per cent. " of eight, or ? five patients.]

Seeing that symptoms of intolerance occur in so many, the author considers that the drug can only be given when the patient can be under constant supervision and it is, therefore, not suitable for mass treatment. He suggests that as his results differ so much from those reported by others, it is possible that the Portugal strain of *S. haematobium* differs from that obtaining elsewhere.

H. Harold Scott

ALVES, W. **The Treatment of Urinary Bilharziasis with Miracil D and Nilodin.** *Ann. Trop. Med. & Parasit.* 1950, Apr., v. 44, No. 1, 34–41. [16 refs.]

Nilodin is the same chemical compound as Miracil D, but is manufactured by Burroughs Wellcome, Ltd., London. A review is given of published reports concerning these drugs ; they have already been abstracted in this *Bulletin.* Considerable importance is now attached to the type of tablets used. Coated tablets have been prepared in order to avoid the unpleasant taste, but it was feared that the coating might hinder absorption of the compound in the intestine. Investigations were therefore undertaken in Southern Rhodesia to examine this point.

In the first group, 43 young adult Africans (school boys) infected with *Schistosoma haematobium* were given 10 mgm. per kgm. twice daily for three days, total 60 mgm. per kgm. The drug was given as sugar-enteric-coated tablets. Twenty weeks later, 17 of the boys continued to pass blood and living eggs, so that the cure-rate was 60·5 per cent.

Group II consisted of 2,605 persons in the Msana Native Reserve, and it was carried out to test the administration of the drug by relatively untrained persons. The population was divided into old adults (over 40), young adults, and children (4–17). Urines from every fifth person were examined. Of these people, 1,600 were given 60 mgm. per kgm. body weight (guessed) as in Group I, coated tablets being used. The disappointing results obtained in Group I then became known, and the remaining 1,005 people were given a total of 100 mgm. per kgm. in three days. The results are shown in the Table.

Showing the results obtained in 2,605 persons treated with nilodin.

Cases	No. treated	Urines examined before treatment	Positive		Urines examined after full course	Positive	
			No.	Percentage		No.	Percentage
		60 mgm. per kgm. body-weight					
"Old adults"	341	45	10	22·2	128	22	17·2
"Young adults"	349	80	35	43·7	193	57	29·5
"Children" ...	910	205	123	60·0	519	269	51·8
		100 mgm. per kgm. body-weight					
"Old adults"	130	29	7	24·1	74	7	9·5
"Young adults"	220	49	13	26·5	93	8	8·6
"Children" ...	655	106	46	43·4	214	60	28·0

These results are disappointing. Of the 2,605 persons who began the treatment, 697 failed to complete it, in spite of adequate propaganda ; probably this backsliding was due to anorexia and constipation produced by the drug.

Group III consisted of 164 mixed persons on a tobacco farm, all of whom received 100 mgm. per kgm. during three days under good supervision. Before treatment the infection rate was 41·7 per cent. Seven weeks later the urines were examined from 136 subjects (including 55 who had previously been positive) and the infection rate was 21·3 per cent. ; 29 of the 55 originally positive cases were still positive, a cure rate of 47·3 per cent. The treatment was

rather unpopular. In a few Europeans treated in Rhodesia, there has been severe mental depression.

The disappointing results obtained in these later trials of nilodin or miracil are probably due to the use of coated tablets. Correspondence with the makers shows that when these enteric coated tablets are given to healthy Europeans, absorption has been perfectly satisfactory. But perhaps the diseased African gut is responsible for less complete absorption when such tablets are used. The successful application of this therapeutic compound in the field probably depends on the discovery of a satisfactory method of administration, which will be acceptable to the patient while permitting complete absorption so as to destroy the worms.

F. Hawking

ALVES, W. **Oral Treatment of Urinary Bilharziasis.** [Correspondence.] *Lancet.* 1950, June 17, 1134.

In this letter, the author records a study additional to that reported above, in which he compared the use of Miracil D, Miracil A, sugar-enteric-coated nilodin and plain nilodin. These drugs were given to four groups of African schoolchildren, aged 6 to 18 years having urinary bilharziasis. The cases were quite unselected. The children lived in a village outside Salisbury, S. Rhodesia, in an area where extensive treatment of streams with copper sulphate had been carried out : for many months they had used only borehole water, so that recent infection was very unlikely.

The dosage and follow-up arrangements were similar to those previously described by the author [this *Bulletin*, 1949, v. 46, 947]. Each child was given 60 mgm. /kgm. body weight of the particular drug, divided into six doses given morning and evening for three days.

The results were as follows :—

Drug	No. of Cases	Results	
		Cures	Failures
Miracil D	40	37	3
Miracil A (Elberfeld) ...	28	13	15
Nilodin plain	68	62	6
Nilodin coated	68	28	40

It is clear that Miracil D and plain uncoated nilodin were " as effective as any known drug in the treatment of urinary bilharziasis ". Miracil A was much less effective and the author is impelled to conclude that the sugar-enteric-coated nilodin tablets are poorly absorbed in the African gut.

H. J. O'D. Burke-Gaffney

HUNTER, G. W., DILLAHUNT, J. A. & DALTON, H. C. **The Epidemiology of Schistosomiasis Japonica in the Philippine Islands and Japan. I. Surveys for Schistosomiasis Japonica on Mindoro, P. I.** *Amer. J. Trop. Med.* 1950, May, v. 30, No. 3, 411–29, 12 figs. (4 maps). [16 refs.]

The invasion of Leyte in October 1944 resulted in the appearance of *S. japonicum* infections among a high proportion of the American troops and, following the realization of the extent and serious nature of the outbreak, an attempt was made to delineate the endemic areas in other islands, including Mindoro, which is the subject of the present paper. This island covers an

area of nearly 4,000 sq. miles, so that the survey was of necessity limited to certain areas, such as San Jose on the south-western plain and the Lake Naujan region on the north-eastern coastal plain, the latter area having been the subject of previous reports by AFRICA and GARCIA (*Philippine J. Pub. Health*, 1935, v. 2, 54) and by TUBANGUI and PASCO (*Philippine J. Sci.*, 1941, v. 74, 301). In both these areas the surveys were preceded by an aerial reconnaissance designed to pick out the more likely-looking areas in which attempts could be made to collect specimens of *Oncomelania quadrasi*, the local intermediate host of *S. japonicum*. The selected areas were then visited, snails collected, identified and dissected, and the nature of their habitat and the *p*H of the water was recorded. At the same time as the molluscan fauna was being investigated, the inhabitants of the neighbouring villages were examined for spleen and liver enlargement, or other evidence suggestive of schistosomiasis. Each person examined was asked to bring a specimen of his faeces on the following day, this appeal being successful in some 80 per cent. of the inhabitants interviewed. "The findings reported were based on a single stool specimen which was examined first by two direct smears and was then sedimented in a half liter pharmaceutical graduate, two smears being made after sedimentation." Later in their paper the authors state that they now consider the recently described "acid-sodium sulfate-ether techniques" to be more reliable than the direct smear and sedimentation method, and they believe that if they had employed one of the latter methods the proportion of persons positive would have been considerably higher. In addition to examining the human population in the areas, stools from dogs, pigs and carabao calves [draft buffalo] were collected and searched for the eggs of *S. japonicum*. The authors' summary and conclusions are as follows :—

"1. Schistosomiasis japonica is endemic in the Naujan municipality of Mindoro, P.I. It was found in approximately 40 per cent of a population sample in 1945 compared to 20 per cent in 1939.

"2. At the time this survey was made the incidence of schistosomiasis japonica increased to a peak in the fourth decade, after which there was a drop in individuals over 40.

"3. In this highly malarious population enlargement of the liver or spleen does not characterize proven cases of the disease, and these physical signs are not suitable for surveying individuals suspected of being infected.

"4. The classical results of portal venous obstruction were encountered in only one-sixteenth of the proven cases of chronic schistosomiasis japonica found in this population.

"5. A hitherto unreported area endemic for *S. japonicum* has been found in Pola municipality, sitio of Casiligon, Mindoro, P.I.

"6. The incidence of infection of intermediate hosts by *S. japonicum* was found to be about 1 per cent of 1622 snails (*O. quadrasi*).

"7. One of six carabao calves, nine of 13 pigs and eight of 14 dogs examined in this area yielded eggs of *S. japonicum* in their stools." *R. M. Gordon*

HSÜ, H. F. **A Preliminary Study on the Bionomics of *Oncomelania* Snails, Intermediate Hosts of *Schistosoma japonicum*, in Kiangsu and Chekiang Provinces, China.** *Amer. J. Trop. Med.* 1950, May, v. 30, No. 3, 397–410, 3 figs. (1 map). [15 refs.]

This paper deals with the bionomics of *Oncomelania hupensis* and *Oncomelania nosophora* as observed in Lower Central China. In the main, the author confirms the early observations of FAUST and MELENEY [this *Bulletin*, 1925, v. 22, 468] ; KAN and YAO (1934) and ABBOTT [this *Bulletin*, 1948, v. 45, 1096] in this area, but differs from the opinion expressed by the latter author who

considered that "In the main, however, *O. hupensis* is responsible for the disease being contracted in the canals". In his—Hsu's—opinion irrigation ditches are the most important habitat for both *O. nosophora* and *O. hupensis*. "Even for the latter species, irrigation ditches are a more favorable place for the snails to thrive and reproduce than the canals. From what I have seen in Pu Yun Chin, Kashing, I could hardly find an irrigation ditch which did not contain *Oncomelania hupensis*. In the canals, on the other hand, no matter what kind of canal it is, this species of snail is either entirely absent or present only in spots. *Oncomelania* collected in Kashing shows definitely the characteristics of *O. hupensis*. As the water in the rice fields comes from the irrigation ditches, I am of the opinion that the rice fields are the chief places where farmers acquire infection. This fact holds true both in the area with *O. nosophora* and with *O. hupensis*. In the area infested with *O. hupensis*, water in the canals is next in point of infectivity, and not first as the source of schistosomiasis infection."

[The author apparently bases this opinion on the relative abundance of the snails in the irrigation ditches, since he makes no reference to any snail dissections having been carried out.] *R. M. Gordon*

Most, H., Kane, C. A., Lavietes, P. H., Schroeder, E. F., Behm, A., Blum, L., Katzin, B. & Hayman, J. M., Jr. **Schistosomiasis japonica in American Military Personnel : Clinical Studies of 600 Cases during the First Year after Infection.** *Amer. J. Trop. Med.* 1950, Mar., v. 30, No. 2, 239–99, 2 figs. [81 refs.]

Over 1,500 members of the American Forces contracted Eastern schistosomiasis on Leyte island, in the Philippine group, between October 1944 and March 1945. The outbreak was almost explosive in incidence ; the first cases appeared within 40 or 50 days of first exposure to infection and they presented the signs of a systemic rather than those of a localized condition. Three fatalities occurred on the island, but treatment rather than the disease may have been the cause of these. After preliminary investigation overseas the patients were concentrated in special hospitals in the United States. The opportunities for observation and investigation, from the first appearance of symptoms until final cure of the condition, were therefore unique. Some reports on these cases while still on Leyte have already been published [this *Bulletin*, 1945, v. 42, 1018, 1019 ; 1946, v. 43, 351, 756 ; 1947, v. 44, 834] ; reports on 484 other patients in a centre in the U.S. have already been published by others [*ibid.*, 1946, v. 43, 1157 ; 1947, v. 44, 732] ; this paper records observations made in the United States on 596 of the patients in a second such centre at Moore General Hospital.

No ova of *Schistosoma japonicum* were recovered from 62 (10·4 per cent.) of the 596 patients of the group under immediate consideration ; the symptoms from which these 62 men suffered were ascribed to infections other than schistosomiasis and so these men were regarded as a non-schistosomal control group ; 89 (14·9 per cent.) of the 596 gave a history and suffered from manifestations suggestive of schistosomiasis, but no ova were found in the stools to establish the diagnosis—nevertheless these men were regarded, on clinical grounds, as suffering from schistosomiasis ; 235 of the men (39·4 per cent.) had been found to be passing eggs in the stools before repatriation to the U.S. ; and 210 (35·3 per cent.) were found actually to be passing ova in their stools after repatriation. Of these last two groups, aggregating 75 per cent. of the total, the first had received treatment overseas and no ova were subsequently found on return home, so they either had been cured or had only "light" infections ; some men of the latter group had been found to be passing eggs

before repatriation from the Philippines where they had been treated, and from the others no ova had been recovered before the men's return to the U.S. When specific treatment was given at this centre there followed a period of at least three months' close observation, during which at least 30 stools were searched for ova ; if ova were again found the patients were re-treated, and further observations and re-examination were undertaken for a similar period.

An analysis is given of the clinical data relating to substantial sections (50 or 100 men) of each of the last three of the original four groups, while under study in the U.S. ; the details are set forth in a series of tables. A study of these shows that of 86 patients who suffered moderate or severe symptoms overseas 32 (37 per cent.) were asymptomatic on repatriation, 36 (42 per cent.) had mild, 18 (21 per cent.) had moderate, and none had severe symptoms. Of 49 other patients proven to be infected while overseas, but stool-negative after repatriation, nearly one-half were asymptomatic some six months after the initial infection. No patients were febrile on repatriation, and in 70 per cent. of them the symptoms were then so slight that the men really need not have been hospitalized. The complaints chiefly ventilated were of weakness and of fatigue, but these may in part have been of psychogenic origin ; abdominal cramp, especially in the right upper quadrant, was another common complaint. There were no physical signs in 60 per cent. of the men of the definitively diagnosed groups ; 18 per cent. had upper abdominal tenderness ; 15 per cent. had a palpable but not grossly enlarged liver, which often was slightly tender ; and 4 per cent. had a palpable spleen. These figures were not significantly different, apart from the enlargement of the liver, from those obtained from the control group of cases.

Seventeen cases with proven, or with presumptive evidence of, localization of *S. japonicum* ova in the central nervous system were found in this series. Details of these, with those of ten other cases, are recorded below ; half of these 27 patients suffered from manifestations suggestive of an expanding intracranial tumour ; from 90 per cent. of them no schistosome ova were recovered from the stools at the time of onset of the neurological signs ; but treatment with antimony, together with intracranial surgery when necessary, restored most of these patients to useful lives. Ova were found in the brain tissue in all 15 of the cases in which biopsy was done. The neurological and histological findings, and changes in the cerebrospinal fluid, are briefly re-stated ; and attention is focused on the possibility of central nervous system complications in further cases of schistosomiasis now in the U.S. during the coming years.

There follows an exhaustive analysis of the laboratory findings in the series of cases under observation, the details of which should be sought in the original. In brief, the generally accepted view is confirmed that the changes in the blood picture seen six months after the infection is acquired do not afford specific help in assessing the severity of the disease or the result of treatment. There was no evidence of renal impairment, and there was little evidence of hepatitis or of impairment of liver function as a result of this particular schistosomal infection. In the early stages of infection, 25 of 46 men examined by sigmoidoscopy, while overseas, had been reported to show "typical" nodules. Sigmoidoscopy in the U.S. of these 46 men, who had already been specifically treated overseas, in one case revealed a schistosomal nodule containing ova, and in another a polyp containing eggs ; in other men it was thought there were minor, but not characteristic, changes in the mucosal surface of the rectum. It is inferred that the submucosal nodules seen sigmoidoscopically, and considered characteristic of the infection, do not persist after adequate specific treatment, and they do not make their appearance in patients found still to be infected at the end of six months.

X-ray examination of the chests of 51 men overseas had shown pulmonary changes in 33 of those who were moderately or seriously ill at the time of onset of the disease ; repetition of the X-ray examinations in the U.S. six months later showed an increase in the normal linear pulmonary markings in seven of these 33 men, but there were no associated subjective complaints. Gastro-intestinal X-ray examinations of 50 proven cases of Eastern schistosomiasis revealed no significant changes throughout the length of the gut. The results of complement fixation tests have already been published [this *Bulletin*, 1948, v. 45, 916] ; these proved to be less of diagnostic than of prognostic value. Intradermal skin tests, with a *S. mansoni* antigen, assisted in the diagnosis in doubtful cases in which no ova could be found ; this test proved highly specific, and no " false positives " were disclosed among the controls.

A firm diagnosis of schistosomiasis rests on finding some stage of the parasite, usually the ova. This was not always possible under the conditions obtaining overseas, but the examinations were easier to perform in the U.S. The results of 25,000 stool examinations, which have been recorded in detail elsewhere [this *Bulletin*, 1947, v. 44, 333], showed that a simple modified water centrifugal sedimentation technique was efficient in disclosing small numbers of viable schistosome ova which escaped other accepted methods of concentration and recovery. To reveal such light asymptomatic infestations examination of from 20 to 30 stools may be necessary over a period of four to six weeks ; to assess the result of treatment stool-examinations should be undertaken 30 days after its completion, and three stools should then be searched each week for eight to ten weeks, as most failures to cure become evident from five to twelve weeks after the completion of treatment.

The methods of treatment adopted for this series of cases were decided on after consideration of the available drugs, and of the published work on the distribution and fate of antimony in the body as revealed by radio-active tracer compounds. The drugs tried included emetine, anthiomaline, Fouadin, and tartar emetic (the potassium salt) ; the dosages of the last two of these were adjusted to provide approximately equivalent amounts of metallic antimony. Emetine was used in only four cases, and it failed to sterilize any of them ; anthiomaline cured every one of the five cases in which it was employed. Fouadin was given, intramuscularly, and the treatment was simple and required no special precautions. Treatment with tartar emetic intravenously needed much care in the preparation of the fresh solution used and in its injection, to forestall toxic sequelae. One or other of two dosage schedules with Fouadin was employed in the treatment of 342 patients ; and there were five dosage schedules with potassium antimony tartrate, in 0·5 per cent. solution in glucose saline or in distilled water, used in the treatment of 74 patients. The various courses of treatment tried with these two drugs are summarized below :—

(1) Fouadin (6·4 per cent. solution) to total of 70 ml. (0·595 gm. antimony) over 27 days. Days 1, 2 and 3—1·5, 3·5, and 5·0 ml. intramuscularly ; and then 5 ml. on alternate days for 12 doses.

(2) Fouadin (6·4 per cent. solution) to total of 100 ml. (0·85 gm. antimony) over 14 days. Days 1, 2, 3 and 4—2, 4, 6 and 8 ml. intramuscularly ; and then 8 ml. daily for ten doses.

(3) Antimony potassium tartrate (0·5 per cent. solution) to total of 290 ml. (0·522 gm. antimony) over 31 days. Days 1, 3 and 5—5, 10 and 15 ml. intravenously ; and then 20 ml. on alternate days for 13 doses.

(4) Antimony potassium tartrate (0·5 per cent. solution) to total of 360 ml. (0·648 gm. antimony) over 29 days. Days 1, 3, 5, 7 and 9—8, 12, 16, 20 and 24 ml. intravenously ; and then 28 ml. on alternate days for ten doses.

(5) Antimony potassium tartrate (0·5 per cent. solution) to total of 360 ml. (0·648 gm. antimony) over 25 days. Days 1, 3 and 5—10, 20 and 30 ml. intravenously ; and then 30 ml. on alternate days for 11 doses.

(6) Antimony potassium tartrate (0·5 per cent. solution) to total of 416 ml. (0·750 gm. antimony) over 33 days. The details are as for (4) but the drug was continued for two additional final doses.

(7) Antimony potassium tartrate (0·5 per cent. solution) to a total of 444 ml. (0·80 gm. antimony) over 35 days. Details as for (4) but continued for one additional dose.

The ultimate results of these various schedules of treatment can be tabulated as follows :—

Treatment	Number treated	Failures to cure
Course (1) ...	42	33 (79 per cent.)
Course (2) ...	64	13 (20 per cent.)
Course (3) ...	51	25 (49 per cent.)
Course (4) ...	79	13 (16 per cent.)
Course (5) ...	52	8 (15 per cent.)
Course (6) ...	50	2 (4 per cent.)
Course (7) ...	12	1 (8 per cent.)
TOTALS	350	95 (27 per cent.)

The intervals after unsuccessful treatment before ova reappeared in the stools ranged from 36 to 176 days ; on the average they were shorter after Fouadin treatment than after tartar emetic treatment. Toxic effects of the various courses of treatment were apparent in 94 per cent. of all patients, though in only 15 per cent. of them were they " moderately severe " ; in less than 1 per cent. had treatment to be discontinued on account of them. Muscular pains, cough, and conjunctivitis were less marked with Fouadin than with tartar emetic, but the former drug caused more nausea and vomiting. Arthralgia became troublesome towards the end of the tartar emetic treatments. Coughing could be minimized by reducing the speed at which intravenous tartar emetic was given, by dividing the dose into two parts with an interval of at least an hour between them, and by giving ephedrine subcutaneously ; nausea was lessened in minor cases of reaction by injecting belladonna beforehand, but continuous vomiting necessitated interruption of the treatment for a day or two ; muscle pains and arthralgia were treated palliatively.

Studies of the eosinophile count after treatment as a rule showed a reduction in the number of eosinophiles after successful treatment but, as previously mentioned, eosinophilia is not an invariable accompaniment of infection. No changes in the heart rate were associated with antimony treatment, and this is in contrast to the statements of other workers that bradycardia results from it. There were transient changes in the electrocardiographic recordings during antimony treatment, but these were restored to normal after varying periods thus indicating the absence of any permanent myocardial damage or impairment of function. The intradermal skin test when initially found positive remained so for the period of observation (30 days) after apparently successful treatment.

In 62 cases of failure to cure with the initial course of treatment the patients received a second course ; nine patients had a third, two a fourth, and one patient a fifth course of treatment. There appeared to be no precise explanation as to

why in some cases a single course was curative and in others repeated courses were needed, but it was thought that the weight of the infection was a probable factor.

The reported rare complications of schistosomal infestations due to the lodgement of ova in a variety of tissues and organs were sought for. Cases with involvement of the central nervous system have already been mentioned. In one of these there was a lesion of the fundus of the left eye, and in another a myocarditis, both possibly of schistosomal origin.

The authors complete their report with a review of the differential diagnosis, the criteria for initial treatment and for re-treatment, the prognosis, and the after care of Eastern Schistosomiasis.

[This paper, in conjunction with others from American sources, has done much to amplify our knowledge of all aspects of Eastern schistosomiasis in persons not subject to constant reinfection.] *A. R. D. Adams*

KANE, C. A. & MOST, H. **Schistosomiasis of the Central Nervous System. Experiences in World War II and a Review of the Literature.** *Arch. Neurology & Psychiatry.* 1948, Feb., v. 59, No. 2, 141–83, 5 figs. [Refs. in footnotes.]

Study of the literature published between 1889 and 1944 discloses that 24 cases of cerebral complications attributable to schistosomal infestations were described before the second world war ; 14 were associated with *Schistosoma japonicum* infestations, the remainder were ascribed to *S. haematobium* (seven cases) or to *S. mansoni* (three cases) parasitization. Review of these cases indicates that while *S. mansoni* and *S. haematobium* tend to cause lesions in the cord, *S. japonicum* more commonly involves the brain. The signs of central nervous system involvement by the former two are thus due to myelitis or compression of the cord, while those due to *S. japonicum* cause a wide range of cerebral manifestations. After the second world war an additional 27 cases of central nervous system involvement by schistosomal parasites have been disclosed ; records of 21 of these have already been published, the present paper adds another five, and yet another is to be published [this *Bulletin*, 1946, v. 43, 1047 ; 1947, v. 44, 600] [other papers are in the Press]. *S. japonicum* infection was very prevalent among American troops operating, in particular on Leyte, in the Philippine Islands.

The history and clinical details of the 21 cases already recorded are recapitulated ; 12 of them have since been re-examined by the authors. Thus the authors have had under their care 17 cases of central nervous system involvement attributable to *S. japonicum* infection (2 per cent. of the 800 cases of Asiatic schistosomiasis studied by them at Moore General Hospital tropical centre). The 27 known cases of schistosomal involvement of the central nervous system among American military personnel constitute roughly 2·3 per cent. of all known cases (1,200) of Asiatic schistosomiasis contracted in the Leyte campaign.

The complications referable to the central nervous system in many infective conditions are commonly attributed to cerebral embolism, but usually the cause is thrombosis. The presence of schistosome ova in the brain may be due to the localization there of parturient female worms, or else to the embolic carriage of eggs from worms elsewhere. Paired worms have been found in the cerebral vessels of experimentally-infected monkeys, though none has so far been recovered from this site in man. Possibly there may be adult parasites in cerebral vessels some distance from the lesions caused by the ova ; alternatively there may be adults in the pulmonary vessels, from which ova could be carried to the brain without passing through the liver or the lung filters. It is difficult

to account for "nests" of eggs in the brain without the close proximity of a parturient female worm. Eggs may cause reaction (*a*) by their physical presence, which results in occlusion of the vessel (*b*) by acting as a foreign protein or (*c*) possibly by the elaboration of a chemical toxin.

In 95 per cent. of 25 cases, of which details are available, the onset of complications referable to the central nervous system was rapid and took place on the average nine or ten weeks after infection; the extremes were four to 22 weeks. Headache was a constant complaint, but as most of these patients were febrile at one time or another the importance of headache, unless localized, was difficult to evaluate as an indication of cerebral involvement. In all cases there were periods of confusion ranging from attacks of petit mal to prolonged periods of unconsciousness often with convulsive seizures. Disorientation, listlessness and apathy were also encountered. The convulsive seizures, which were sensory, motor and psycho-motor, were associated with a variety of other disturbances which included motor aphasia, defects in the visual fields, speech disturbances and monoplegia, hemiplegia, or quadriplegia.

The clinical features of the 25 cases are listed in tables. The specific diagnosis of cerebral schistosomiasis is based on the history and on the physical and laboratory findings. The latter may be misleading, as in 90 per cent. of the cases in the present series no ova were found in the stools at the time of the onset of cerebral symptoms. The appearance of neurological manifestations in a patient from a schistosomal endemic area should arouse suspicion that schistosomiasis is the cause of them. In the case of *S. japonicum* the brain rather than the spinal cord is the seat of the trouble, and the motor rather than the sensory tracts are those principally involved. The symptoms commonly are those of a unilateral or a bilateral pyramidal tract syndrome, though encephalitis, meningitis or an expanding intracranial lesion may be simulated. Operative interference is of value to relieve increasing intracranial tension or to remove a lesion causing gross localized irritation. There was only one fatality in the 27 cases recorded in American troops during the second world war, and this man did not die of complications referable to the central nervous system. Cerebral schistosomiasis, although disabling for long periods, is rarely fatal.

The authors give the following summary and conclusions :—

"Involvement of the central nervous system in cases of schistosomiasis is an uncommon complication, but a clinical and pathologic entity, which is due to the presence of the ova of S. mansoni, S. haematobium or S. japonicum within the brain or the spinal cord.

"Twenty-four cases of this condition had been reported in a period of fifty-five years prior to the landing of American troops on Leyte, in the Philippines, on Oct. 20, 1944, and these cases are reviewed in the present paper.

"Experience obtained during nineteen months of World War II, from Oct. 20, 1944, to May 1, 1946 has made it possible to study an additional 27 cases of schistosomiasis japonica, 17 of which have been under observation at this hospital from three to twelve months during the first year and one-half after onset of abnormalities referable to the central nervous system.

"In 22 of these cases, the evidence for the neurologic diagnosis is clinical only, although highly presumptive, there being no mortality in the group. In the remaining five cases, the diagnosis rests on firm pathologic grounds, since the characteristic ova were observed in sections taken from the central nervous system at operation.

"The diagnosis of schistosomiasis japonica is based on the presence of one or more of the following points : (a) a reliable history of exposure to potentially infected fresh water in a known endemic area (China, Japan, Formosa or the

Philippines ; (b) the presence of fever, malaise, generalized aching, cough, headache, anorexia, nausea, vomiting, diarrhoea, progressive loss of weight, urticaria or angioneurotic edema with abdominal tenderness and enlargement of the liver ; (c) the observation of leukocytosis, with a high eosinophil count in the peripheral blood smear, and characteristic sigmoidoscopic findings.

" Involvement of the central nervous system is manifested by a more or less sudden onset of paralysis or weakness of one or more extremities, diffuse encephalitic signs or focal epileptic attacks.

" Pathologically, the lesions of schistosomiasis are due almost entirely to the presence of the ova of the trematodes, which in the case of S. japonicum show a remarkable predilection for localization within the brain (cortex, subcortex, internal capsule and basal ganglia), and in the case of S. mansoni and S. haematobium have been reported to localize only in the spinal cord.

" Microscopically, the pathologic process is one of intense reaction around the ova, with edema, necrosis, cellular infiltration (including foreign body giant cells), phlebitic changes and degeneration of the surrounding neural parenchyma.

" Careful and repeated examinations of the stools are important in establishing the clinical diagnosis, but specific treatment should not be delayed if there is adequate presumptive evidence for the diagnosis, even though all examinations of the stool may be negative for the ova up to the time of onset of abnormalities of the central nervous system.

" Examination of the spinal fluid has not proved of diagnostic significance except in cases with symptoms suggestive of an expanding intracranial process in which increased cell counts and abnormal values for the total protein are commonly found.

" The chief neurologic features of these cases are as follows : (a) with S. mansoni and S. haematobium, syndromes mainly of spinal cord origin, i.e., transverse myelitis ; and (b) with S. japonicum, (1) monoplegias, hemiplegias or quadriplegias of cortical, subcortical or capsular origin ; (2) diffuse encephalitis and/or meningitis, and (3) syndromes simulating tumor of the brain.

" Operative intervention may be indicated in cases with focal epileptic seizures, and prompt institution of adequate specific treatment (intravenous injection of 2·22 Gm. (total) of antimony potassium tartrate U.S.P.) is recommended in all cases in order to prevent further localization of ova within the central nervous system.

" The immediate prognosis for life in cases of this condition is good, but mild to severe neurological residual disturbances may be expected in a significant proportion of cases for at least one year after the time of onset.

" Further cases may occur in occupation troops stationed in the Far East or among veterans who have served in endemic areas.

" Cerebral schistosomiasis will continue to demand a high degree of clinical awareness, since it may appear not only in cases in which there is a definite history of schistosomiasis but in any case in which there has been exposure to the infection, even after a 'silent' or latent phase, which may be as long as two to four years."

The authors conclude with an appendix in which accounts of six illustrative cases are set out in detail. *A. R. D. Adams*

HARLAND, J. C., HUMBLE, J. G. & MANN, P. G. **Diphyllobothrium Infestation and Anaemia in Great Britain.** *Brit. Med. J.* 1950, July 22, 188–92, 6 figs. [19 refs.]

The authors discuss the incidence, geographical distribution, development and symptomatology of *Diphyllobothrium* infestation. They stress in particular

the characteristic megaloblastic anaemia and its relative frequency among those of Finnish stock compared with those of other descent. Reference is made to the work of BONSDORFF, HERNBERG and others, with which readers of this *Bulletin* will be familiar.

Human infestation with *Diphyllobothrium* is almost unknown in Great Britain, although *D. latum* has been known in Ireland for over 100 years. Nevertheless, related fish tapeworms have been recorded more recently in Wales [this *Bulletin*, 1944, v. 41, 857]. The parasite is now firmly established in parts of the United States and Canada and is endemic there [as STILES predicted over 40 years ago] : it would seem that the worm had not been indigenous there for more than a short time and was probably imported by immigrants from the Baltic States.

The present authors report the case of a Finnish domestic servant of 22, who had lived in England in good health for two years. She then developed an anaemia which was at first tentatively diagnosed as pernicious anaemia. One injection of liver was given, but the patient soon left the neighbourhood.

She was first seen by the authors two months later. Apart from pallor, there were no significant physical signs. Haematological examination showed the presence of a megaloblastic anaemia. Full details of the blood examination are given, which show that the bone-marrow appearances were atypical : this is attributed to the original liver injection. A histamine-fast achlorhydria was present.

On clinical grounds, steatorrhoea and pernicious anaemia were excluded from the diagnosis, and in view of the patient's nationality, stool examinations were made for *Diphyllobothrium*. Ova were found in three successive stools.

The patient was treated with extract of male fern (5·4 ml. in three divided doses) and two adult worms were expelled, one with the head intact : they were identified as a species of *Diphyllobothrium*. A reticulocytosis began nine days later and continued for four days. An injection of " anahaemin " a few days later produced no more reticulocytes, but the anaemia improved rapidly and the patient was discharged a few weeks later. Three months later she was well and her stools were free from ova.

The ova measured $68\,\mu \times 48\,\mu$ and the adult worm was 6 metres long. These are illustrated in four photographs.

In an addendum, the authors refer briefly to another case in a Finnish woman of 34, who had been in England for three and a half years. She had often been infested with tapeworms since the age of ten and had noticed segments in her stools a few months before. For some weeks she suffered from postural dizziness, a symptom she associated with the presence of the worms, but her blood count was normal. *Diphyllobothrium* ova were present in the stools. Disinfestation has not yet been carried out.

In discussing the public health aspects of the subject the authors, quoting the American experience, point out that the increase in immigrants from heavily infested areas might result, in rural areas with primitive sanitation, in contamination by carriers of fish-bearing waters, with ultimate human infestation. They quote official figures to show that early in 1942, the number of Esthonian, Latvian and Lithuanian nationals living in Britain was 3,212 : by late 1949, the number was 26,745. Also, the number of Finns has increased from 447 in 1939 to 1,208 in 1949.

The question is discussed further in an authoratitive annotation in the same number of the *Journal*, which concludes that the present authors " rightly emphasize the need for further investigation by the public health authorities."

H. J. O'D. Burke-Gaffney

PHAM-NGOC-THACH. Syndrome de Löffler récidivant et s'accompagnant d'hémoptysies fugaces chez un porteur de *Taenia saginata*. [**Relapsing Loeffler's Syndrome with Transient Haemoptysis in a Carrier of** *Taenia saginata*.] *Rev. Méd. Française d'Extrême-Orient.* 1942, June–July, v. 20, No. 6, 829–34, 1 pl.

PANSINI, R. & PIRASTU, C. Rivista sintetica di aggiornamento biologico-morfologico-etiopatogenetico sulla malattia idatidea. [**Review of the Literature on the Biology and Pathogenesis of Hydatid Disease.**] *Arch. Ital. Sci. Med. Trop. e Parassit.* 1950, Feb., v. 31, No. 2, 107–67. [Bibliography.]

LIPPI, M. Nuove ricerche sull'eosinofilia midollare nell'echinococcosi. [**New Observations on Eosinophilia in the Bone Marrow in Echinococcal Disease.**] *Arch. Ital. Sci. Med. Trop. e Parassit.* 1950, Feb., v. 31, No. 2, 93–106.

The English summary appended to the paper is as follows :—

"Eosinophilia in the bone-marrow of 37 persons affected by echinococcus cysts (first mentioned by Girolami) was observed to be present in all cases, even when it did not appear in the peripheral blood and when the intradermal test (Casoni) and the Ghedini-Weinberg (complement-binding) test were negative.

"This appeared to be even more evident when the eosinophils instead of being calculated as a percentage of all elements contained in the myelogramme (myeloblasts and erythroblasts) are calculated in proportion only of the myeloblasts.

"This is of great value for the diagnosis of the disease if other affections also causing eosinophilia in the bone marrow may be excluded."

LÓPEZ-NEYRA, C. R. La *Tenia madagascariensis* Davaine 1869, oriunda cubana, y el *Inermicapsifer cubensis* (Kouri, 1939) son una misma especie, correspondiente al genero Raillietina (Fuhrmann, 1920) Lopez-Neyra 1934. [*T. madagascariensis*, **Davaine 1869 and** *I. cubensis* (**Kouri, 1939**) **are One Species of the Genus** *Raillietina* (**Fuhrmann, 1920**) **Lopez-Neyra, 1934.**] *Rev. Ibérica de Parasit.* 1950, Apr., v. 10, No. 2, 187–203.

Those interested in solving the intricate puzzles of helminth nomenclature will find here a problem to delight them. Tracing the records for the past 80 years and discussing them—the paper is fully documented—the author concludes that 15 species of *Raillietina* which have been described in and from various parts of the world are reducible to four, namely, *R. madagascariensis* (Davaine, 1869) of which *Inermicapsifer cubensis*, *R. davainei*, *R. loechesalavezi*, and *Kouridovali* are synonyms ; *Raillietina demerariensis* with *R. quitensis* and four of Dollfus as synonyms ; these are American species ; while oriental species are *R. formosana* and *Meggittia celebensis*, which, strictly, it is said, ought probably to be called *R. asiatica*. These last two have been called *Davainea madagascariensis*, but wrongly. All these are discussed fully.

The author concludes by saying that "if we consider afresh the 14 species which make up the genus *Inermicapsifer*, and for differentiation of which the author puts forward a simple key, we shall see that, excluding the Cuban species by showing that it belongs to the genus *Raillietina* the rest comply with the characteristics set forth by Janicki in 1910 . . . and the genus *Inermicapsifer* should be transferred to *Raillietina*, leaving at present undefined the exact position of *Inermicapsifer* until the larval states, the transmitters and the complete life-cycle are discovered." *H. Harold Scott*

GALLIARD, H. Pluralité des races de *Strongyloïdes stercoralis* d'origine humaine. Mesure de leur virulence par le test du pouvoir infestant expérimental. (Note préliminaire.) [**Multiplicity of Races of *Strongyloides stercoralis* of Human Origin. Virulence Tests as adjudged by Experimental Infecting Power.**] *Rev. Méd. Française d'Extrême-Orient.* 1942, May, v. 20, No. 5, 599–602.

HÖTZ, Maria & BROSCHEIT, A. Nachweis von Wurmeiern durch einfache Papierfiltration. [**Recognition of Helminth Ova by Simple Filtration through Paper.**] *Gesundheits Ingenieur.* 1950, June, v. 71, Nos. 11/12, 185–6.

As is well known the usual methods of finding helminth ova are : 1. Direct examination of the material under the microscope ; 2. The salt-floatation method ; 3. Centrifugation before microscopic examination ; 4. By culture. But, when the material is not likely to contain many ova, as in waste-waters, ordinary filtration answers very well. At first, thin layers of wadding were used, as suggested by EUGLING ; later, membrane filtration as used by G. MÜLLER, but the authors find that ordinary filter-paper is rapid, convenient, cheap and quite efficient. The material is drawn through filters into a flask by a suction-pump. The paper can be examined at once or even weeks later and if the filter becomes quite dry and is no longer transparent, it can be made so by moistening again with water. By using a measured quantity of the original fluid, the method becomes a quantitative and not merely a qualitative one. *H. Harold Scott*

STUTZ, L. Ueber den Einfluss der Klärschlammtrocknung nach dem " Elka "-Verfahren auf die Askarideneier. [**Effect of Drying of Waste Products by the " Elka " Process on the Content of *Ascaris* Ova.**] *Gesundheits Ingenieur.* 1950, June, v. 71, Nos. 11/12, 184–5.

In Darmstadt waste water (and sewage) has been dried by the " Elka " process and used as fertilizer. The question arose as to what effect the drying has on the content in *Ascaris* ova. By this process, the waste is led on to drying fields and air-dried until it is fairly firm and is then spread out in layers for further drying. As soon as the cakes become hard they are placed in " ferment heaps " and in them a temperature of 70°C. is reached ; the product is then ground and used as fertilizer.

By direct examination of the Mannheim sewage, without enrichment, very few ova were found—six in 27 preparations of about 0·05 cc. Direct stool examination of 796 persons revealed that only 11 were passing ova of *Ascaris lumbricoides*, 1·4 per cent. The results of examining a loopful (0·05 cc.) of the product at different stages are given in a table. Fresh, as spread out to dry, two ova ; at the beginning of the drying, 12 ; at the middle, 26 ; at the end, eight ; in the spread-out layers, six ; in the ferment heaps four to eight ; in the end-product, six ; later, in the winter, one, and in the following May, none. Thus, by the Elka process in the warm months of the year *Ascaris* ova are killed. *H. Harold Scott*

ZSCHUCKE, J. Zur Frage der Behandlung der Spulwurminfektion mit Bedermin. [**The Treatment of Ascariasis with Bedermin.**] *Deut. med. Woch.* 1950, June 16, v. 75, No. 24, 839–40.

Bedermin is a mixture of Ascaridole (one part) and a carbon tetrachloride preparation (six parts) [see this *Bulletin*, 1950, v. 47, 258]. The taking of Bedermin is not devoid of danger and fatal effects have been recorded, the post mortem findings indicating poisoning by CCl_4 or its split-products. How far this is the result of innutrition of the patient or a " tendency to anaphylaxis "

or to racial susceptibility is not certain. In the author's view Ascaridole in a single dose of 0·015 to 0·018 gm. per kilo body-weight, in gelatin capsule, or in a 2·5 per cent. solution in castor oil is best in general, with ol. ricini or a saline purge, the patient being kept under observation until the purgative has acted. If there is no motion in two hours the purgative should be repeated. Bedermin should be reserved for special cases and should never be used after prolonged storage. *H. Harold Scott*

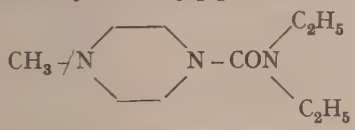
BHATTACHARJEA, S. K. **An Unusual Case of Elephantiasis Buttocks.** *Indian Med. Gaz.* 1950, Apr., v. 85, No. 4, 158, 2 figs. on pl.

HUARD, P. Les lésions génito-urinaires des filariens. [**Genito-Urinary Lesions in Filariasis.**] *Rev. Méd. Française d'Extreme-Orient.* 1941, July–Aug., v. 19, No. 7, 768–82, 4 figs. [Numerous refs.]

ALVES, J. B. de R. & RIBEIRO, L. A. Tratamento cirúrgico da elefantíase. [**Surgical Treatment of Elephantiasis.**] *Hospital.* Rio de Janeiro. 1950, May, v. 37, No. 5, 729–45, 22 figs. [33 refs.]

HAWKING, F., SEWELL, P. & THURSTON, June P. **The Mode of Action of Hetrazan on Filarial Worms.** *Brit. J. Pharmacol. & Chemotherapy.* 1950, June, v. 5, No. 2, 217–38, 6 figs.

Hetrazan, 1-diethylcarbamyl-4-methylpiperazine



was found by HEWITT *et al.* [this *Bulletin*, 1948, v. 45, 454] to exert an anti-filarial action on *Litomosoides carinii* in cotton rats and on *Dirofilaria immitis* in dogs, and by SANTIAGO-STEVENSON *et al.* [*ibid.*, 1948, v. 45, 353] in human filariasis. In the present experiment, rats were infected by the mites *Liponyssus bacoti* and about 70 days later were treated by hetrazan intraperitoneally according to various dosage schedules, when microfilariae were present in the blood. A marked but somewhat irregular reduction in numbers took place and even with doses approaching the maximum tolerated all microfilariae did not disappear from the blood, even when administration was continued for 108 days in drinking water. The decrease in numbers was soon followed by a rise in absence of treatment. The adult worms were but little affected.

For *in vitro* studies microfilariae were separated from blood by differential centrifugation under aseptic conditions and kept in small vessels resembling Carrel flasks in which the parasites could be kept under observation by means of an inverted microscope. Different fluids were added through a side arm and it was found that rat serum one volume with Tyrode solution four volumes was most satisfactory for maintenance. Hetrazan in a concentration of 4 mgm. per ml., or serum from rats which had received maximal doses of the drug, was found to exert no deleterious effects.

Treatment *in vivo* by the intraperitoneal route, on the other hand, caused rapid disappearance of microfilariae from blood and when it was given intravenously 95 per cent. of them disappeared within two minutes, although complete clearance was not effected. It was shown that this persistence was due to the presence of the microfilariae in the pleural cavity whence they migrated *via* the lung to the circulating blood. To determine the fate of the microfilariae which had left the blood, untreated rats and those receiving

250 mgm. hetrazan per kilo intraperitoneally were investigated by estimating the numbers per unit area in stained sections and then in unit volume by use of a conversion factor. In untreated rats 63 per cent. of microfilariae were in blood, 30 per cent. in lungs and 2·6 per cent. in both liver and kidney, negligible numbers being present in other organs. After hetrazan treatment the blood level fell markedly while the numbers in liver increased greatly, but those in kidney were little affected. Calculation indicated that the number disappearing from the blood was correlated with those appearing in the liver. This rise in number in the liver was maintained for some hours, with subsequent decline to the original level within 24 hours, but without corresponding increase in blood. It was therefore assumed that the microfilariae migrating to the liver had been killed. Histological examinations of this organ revealed that after drug treatment phagocytosis of the parasites was marked and it was concluded that hetrazan has an opsonin-like action. Destruction of the parasites by the reticulo-endothelial system of spleen and bone marrow occurred to a lesser degree. As opposed to fixed macrophages those free in the pleural cavity appeared to play little part in the destructive process. Splenectomy combined with intravenous injection of colloidal copper did not prevent hetrazan from exerting its usual effect. Experiments with cataphoresis and those designed to find if other drugs exerted an interference effect yielded little information. TERZIAN [this *Bulletin*, 1948, v. 45, 767 ; 1949, v. 46, 609] showed that the development of malaria parasites in mosquitoes was prevented by certain drugs. When this type of experiment was repeated with a dog parasite *Dirofilaria repens* developing in *Anopheles maculipennis atroparvus*, no effect by hetrazan was noted. Some evidence was obtained that the drug acts on the infective larvae of *L. carinii* : immature female worms were not affected *in vivo* by hetrazan, but it seemed that immature males were affected to some extent. Neostam was effective against all stages in the rat. *J. D. Fulton*

LUBRAN, M. **Determination of Hetrazan in Biological Fluids.** *Brit. J. Pharmacol. & Chemotherapy.* 1950, June, v. 5, No. 2, 210–16, 4 figs.

The introduction of piperazines for the treatment of filariasis was described by HEWITT *et al.* [this *Bulletin*, 1948, v. 45, 454]. The most active of these substances was hetrazan, 1-diethylcarbamyl-4-methylpiperazine. The present author has applied the general methods of BRODIE and UDENFRIEND [*ibid.*, 1947, v. 44, 793] to the determination of this substance in blood and urine of seven volunteers. The method depends on the combination of the base with a suitable dye, in this case bromthymol blue, to form a salt which is then extracted with ethylene dichloride ; optical densities are determined in a Spekker photo-electric absorptiometer, or by adaptation of the method, colour intensities are compared with standards in a visual colorimeter. Blank values for normal serum did not exceed 1 gamma per ml. of plasma or serum but were somewhat higher for whole blood. Recovery was satisfactory only when deproteinization was omitted. Probably on account of the amines present the blank values in urine sometimes corresponded to 10 gamma per ml. The addition of a small drop of carbon disulphide followed by extraction with alkali reduced the blank value and did not remove hetrazan. Estimations were performed in ambulant patients treated orally with single or repeated doses of the drug. Patients receiving 6 to 10 mgm. base per kgm. orally had about 1 to 5 gamma per ml. blood in which it was detectable for 24 hours, whereas soon after administration 4 to 8 mgm. per hour was excreted in urine for a number of hours and some was detectable for two to three days. A dosage of 15 mgm. per kgm. caused unpleasant symptoms. After repeated dosage twice daily for five days to a total

of 250 mgm. comparable results were obtained. About 30 per cent. of the administered drug was excreted in the urine. *J. D. Fulton*

HEWITT, R. I., WHITE, E., HEWITT, D. B., HARDY, S. M., WALLACE, W. S. & ANDUZE, R. **The First Year's Results of a Mass Treatment Program with Hetrazan for the Control of Bancroftian Filariasis on St. Croix, American Virgin Islands.** *Amer. J. Trop. Med.* 1950, May, v. 30, No. 3, 443–52, 1 fig. [16 refs.]

This is the second report on an investigation, the first report of which was abstracted in this *Bulletin*, 1950, v. 47, 387. St. Croix is an island in the West Indies with a population of about 13,000. A preliminary survey of 977 persons in 1948 showed 15·9 per cent. with microfilariae in the blood. In 1948, hetrazan citrate was distributed to 105 control patients at a dosage of 100 mgm. for adults and 45 mgm. for children. Eleven people took this daily for five days, the others took it thrice daily for three to seven days. Swallowing of the tablets was unsupervised. One month later 18 to 53 per cent. of the patients were negative for microfilariae and the percentage reduction in the total microfilaria count was 85 to 94 ; one year later, 73 to 88 per cent. were negative and the total microfilaria count was reduced by 96 to 99 per cent.

It was decided that thrice daily dosage for seven days would probably give the best results for the whole population. During June 1948 tablets for self-treatment on these lines were issued to all the inhabitants, together with much relevant propaganda. In general the treatment was well tolerated and no serious reactions developed. In June 1949 a re-survey was made of 471 persons, and 6·7 per cent. were positive for microfilariae and the reduction of the total microfilaria count was 89 per cent. In 1948 the counts went up to 360 microfilariae per 60 cmm. In 1949 the highest count was only 14 microfilariae for 60 cmm. In a home for the aged, blood films had been taken in 1948 from 134 inmates and 18·6 per cent. were positive, the total number of microfilariae (in 60 cmm. samples) being 699. All were treated with hetrazan under good supervision. When revisited in 1949, 92 of the original patients were still present ; the reduction of positives among them was 82 per cent. (*i.e.*, from 23·9 per cent. to 4·3 per cent.) and the total microfilariaemia was reduced by 98·6 per cent. It is claimed [with justification] that the use of hetrazan provides the most practical simple and convenient method for reducing the reservoir of microfilariae available to maintain the infection in a community.

F. Hawking

RAGHAVAN, N. G. S. & KRISHNAN, K. S. **A Note on Experimental Infections of *Mf. malayi* Brug in *C. fatigans* and *A. stephensi* (Type).** *Indian J. Malariology.* 1949, June–Sept., v. 3, Nos. 2/3, 249–52.

"1. Experimental infections of *Mf. malayi* in *Culex fatigans* Weid., 1828, are characteristically negative. This corroborates the findings of Lichtenstein (loc. cit.) in Borneo, and Iyengar (1932) in N. Travancore.

"2. In *M. annulifera* used in the experimental infections of *Mf. malayi*, the infections underwent the normal course of development to their infective stage, i.e. infective larvae in head/proboscis.

"3. Experimental infections of *Mf. malayi* in *A. stephensi* (type) were equally refractory as in *C. fatigans*.

"4. It is suggested that the refractoriness of experimental *Mf. malayi* infection in *A. stephensi* (type) might be used as a diagnostic feature of the infection."

RENJIFO-SALCEDO, S. & ORDUZ-DUARTE, A. Dieciocho nuevos casos humanos, autoctonos, con *Mansonella ozzardi* en Oriente de Colombia. [**Eighteen New Autochthonous Human Cases of** *Mansonella ozzardi* **in Eastern Colombia.**] *Rev. Acad. Colombiana de Ciencias Exactas, Fisicas y Naturales.* 1950, May, v. 7, No. 28, 548. English summary (4 lines).

TENDEIRO, J. Algumas microfilárias dos animais da Guiné. [**Some Microfilariae of Animals in Portuguese Guinea.**] *Anais Inst. Med. Trop.* Lisbon. 1949, Dec., v. 6, 165–227, 16 text figs. & 24 figs. on 12 pls. [85 refs.] English summary.

OVAZZA, M. Quelques observations sur la biologie et plus particulièrement le cycle de *Liponyssus bacoti* Hirst, 1913. [**Some Observations on the Biology of** *Liponyssus bacoti* **Hirst, 1913, with special reference to its Life Cycle.**] *Ann. Parasit. Humaine et Comparée.* 1950, v. 25, No. 3, 178–87, 2 figs. [26 refs.]

This paper contains some useful quantitative data for the tropical rat mite *Liponyssus bacoti* [Parasitiformes, Dermanyssidae]. The life cycle from egg to egg is about ten days at 25°C. and 80 per cent. relative humidity. The length of the cycle is the same at 30°C. and between 75 and 90 per cent. relative humidity. At 18°C. and 65 per cent. relative humidity its duration is 28 days. The adult female may take up to four blood meals and lays a batch of eggs after each meal. The mean numbers of eggs laid by each female after these four meals were, respectively, 13·5, 8·5, 4·7 and 4·7 in the author's studies. The figure of 13·5 was exaggerated because 3·2 per cent. of the 220 females used laid 19 eggs. If these are excluded the mean becomes 11·2. Because of an unavoidable loss of mites at each meal successive means are based on smaller samples. The maximum number of eggs laid in the life of one female was 34. Oviposition occurs on the second and third days after the meal and does not last longer than 27 hours at 25°C. If the temperature is raised to 30°C. the quantity and rate of egg laying remain the same ; similarly raised humidities do not have any effect. Lowering the temperature to 18°C. prolongs egg laying to 72 hours but the same number of eggs are laid. Few eggs are laid at temperatures less than 12°C. The number of eggs laid is markedly reduced at humidities below 65 per cent. relative humidity, and at this humidity no female took a second blood meal.

The incubation period of the eggs is 23 to 25 hours at 25°C., 48 hours at 18°C. and 72 hours at 12°C. all at 80 per cent. R.H. At 65 per cent. R.H. incubation lasts 38 to 50 hours and there is a 50 per cent. mortality. The succeeding larval stage lasts nine to ten hours at 25°C., and 80 per cent. R.H. Lowering the temperature to 18°C. or the humidity to 65 per cent. prolongs the stage to 20 to 25 hours.

The author has found that if fed adults and fed nymphs are placed in a temperature gradient half of them collect between 24°C. and 26°C. and the rest are dispersed between 14 and 30°C. He has found no evidence of a negative geotaxis as suggested by HAWKING and SEWELL [this *Bulletin*, 1949, v. 46, 386], and suggests that mites climb out of the culture jar as a response to the lid being opened. If mites are placed in one limb of an H-shaped tube and a baby mouse in the other they find the host and gorge within 15 minutes. This time does not alter with temperatures from 18 to 30°C. but is prolonged to six hours at 65 per cent. R.H.

The paper closes with a description of the larva complementary to that of HOLDAWAY (*Trans. & Proc. Roy. Soc. S. Australia*, 1926, v. 50, 85).

J. H. Sudd

SEWELL, P. & HAWKING, F. **Chemotherapy of Experimental Filariasis.** *Brit. J. Pharmacol. & Chemotherapy.* 1950, June, v. 5, No. 2, 239–60. [15 refs.]

The use of the cotton rat naturally infected with the filarial worm *Litomosoides carinii* for testing possible chemotherapeutic agents has been described by CULBERTSON [this *Bulletin*, 1944, v. 41, 772]. The successful transmission to cotton rats and white rats of this parasite by the tropical rat mite *Liponyssus bacoti* was accomplished by WILLIAMS and BROWN [*ibid.*, 1946, v. 43, 663, 1080 ; 1948, v. 45, 629]. Later SCOTT *et al.* [*ibid.*, 1947, v. 44, 447, 839, 840] described in detail a method of producing infections in cotton rats so that quantitative chemotherapeutic studies became possible. Experiments have been made in Britain by KERSHAW & BERTRAM [*ibid.*, 1949, v. 46, 69] and by the present authors [*ibid.*, 386]. In the experiments described here about 2,500 cotton rats have been exposed to mites infected with *L. carinii*, with the result that about 80 per cent. had microfilariae in their blood approximately 60 days after exposure. Spontaneous disappearance of microfilariae from peripheral blood is uncommon, but dead adult worms may be found in the pleura of rats with long-standing infections. The most noticeable pathological lesion in these infected cotton rats was enlargement of the spleen and some thickening of the pleura.

The drugs tested were first examined for chronic toxicity in mice and the maximum tolerated dose after four intraperitoneal injections on successive days was determined. The dosage used for cotton rats was 0·4 to 0·5 of that amount calculated on a weight basis. Two rats were treated intraperitoneally with each drug at different dose levels daily for six days. The effect on circulating microfilariae was judged in each case by blood examination before and after treatment. About one week after treatment ended the rats were killed and the pleural contents examined for the presence of live or dead adult worms as well as for microfilariae. The authors consider that female worms are more susceptible to drug action than males, and drug activity was measured by the proportion of females killed by treatment. When activity was evident at a particular dosage level further tests were made. In all, 220 compounds of widely different chemical character were tried [details should be consulted in the original]. No significant activity was found in any of them not already tested by other workers. It was known that antimonials were active against adult worms and this fact was confirmed. Tartar emetic proved an exception. The activity of the other compounds tested varied widely. Only hetrazan [see above] and the substance $Me_2N.CH_2.CH_2.N\ Me.\ CON\ (C_2H_5)_2$ acted on circulating microfilariae, the latter only to a slight degree. *J. D. Fulton*

RAGHAVAN, N. G. S. & MISRA, B. G. **A Preliminary Note on Experimental Infections of Avian Malaria and Sauropsidal Filariasis in *C. fatigans* Weid., 1828.** *Indian J. Malariology.* 1949, June–Sept., v. 3, Nos. 2/3, 243–7.

" There is no antagonism between avian malaria and reptilian filaria infections developing in the same specimens of *C. fatigans* Weid., 1828."

STEFANOPOULO, G. J. **The Symptomatology, Diagnosis and Treatment of Filariasis due to *Loa loa*.** Reprinted from *B.M.A. Proc. Ann. Meeting 1949.* pp. 283–7, 2 figs.

Filariasis due to *Loa loa* is very common among the white population of French Equatorial Africa, and during the past 15 years it has been possible to follow up nearly 500 cases in Paris alone.

During the period of invasion symptoms may be entirely absent, but a proportion of the patients exhibit slight fever, pains in the limbs, sensory changes,

such as paraesthesiae, together with pruritus, which is sometimes associated with an urticarial eruption. After some weeks or even months the disease becomes fully established, and the classical symptoms, which are usually due to the presence of adult worms, but may be due to microfilariae, usually appear. The wandering habits of *L. loa* may cause a wide variety of symptoms and it is not surprising that erroneous diagnoses are often made. On the other hand some of the lesions due to *L. loa* may be ascribed to other causes, and the author suggests that certain cases of hemiplegia and disseminated sclerosis observed in patients with loiasis may be due to the presence of adult worms or to the local action of the microfilariae. The general health of the patient is nearly always affected, and the loss of weight and anaemia, which the author attributes to the effect of toxins derived from the worms, may be considerable. Leucocytosis with an eosinophilia of 15 to 30 per cent. is usual, and the latter count may be as high as 80 per cent.

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Attention is drawn to the fact that many of the patients examined were suffering from malaria, and that this complication added to the difficulties of diagnosis, particularly as microfilariae were seen in the blood in only about 20–30 per cent. of the cases. Intradermal and complement fixation reactions with antigens prepared from *Dirofilaria immitis* or *Litomosoides carinii* [misprinted in the original as *Liponyssus carinii*] have proved of great value in establishing a diagnosis in obscure cases.

The author confirms the successful results with the use of Hetrazan, which were first described by him with Schneider in 1947. [See this *Bulletin*, 1949, v. 46, 275. This review concerns a paper published in 1948. The reviewer can find no reference to any earlier paper by these authors.] Hetrazan is of low toxicity and in the amounts used in therapeutic doses causes no reaction in normal persons, but in persons suffering from loiasis certain phenomena occur, which are due apparently to the action of the drug on the adult worms and embryos in a patient already sensitized to filaria. Fever and nausea may occur, but the most common reaction is a re-activation of filarial lesions, as shown by oedema at the usual sites, and by pruritis, sometimes associated with a

generalized eruption. These lesions appear after the first administration of the drug and they disappear despite the continuation of treatment. To avoid these reactions the author recommends a special course of treatment which is fully described in his paper. "After the first course of injections all symptoms disappear rapidly and the patient believes himself cured, but in the majority of cases after some days or weeks the old symptoms begin again, though with decreased intensity. Only very rarely are microfilariae seen in the blood stream during these relapses. On repeating the curative course there is a gradual disappearance of all symptoms, and some patients have now remained free from symptoms for nearly a year after the cessation of all treatment. Altogether nearly 50 patients have been treated with Hetrazan in the manner described; all with one or two exceptions have become asymptomatic and there is good reason to think that a considerable number have been actually cured, although still further periods of observation are necessary to confirm this impression."

The author suggests that Hetrazan might be used prophylactically, but further observations are required to determine the period for which chemoprophylaxis is effective. *R. M. Gordon*

EICHHOLTZ, F., HOTOVY, R., SAUER, A. & WEISSFLUG, Irene. Egressin, ein neues Chemotherapeutikum gegen die Oxyureninfektion beim Menschen. [**Egressin, a New Drug for the Treatment of Enterobiasis (Oxyuris Infection) in Man.**] *Deut. med. Woch.* 1950, June 23, v. 75, No. 25, 868–70. [13 refs.]

Egressin (Merck) is N-isoamylcarbaminic acid-3-methyl-6-isopropyl-ester. Its chemical formula is given. It is crystalline and colourless with a very slight odour of its own to which is added a slight smell of thymol. It is easily soluble in organic solvents, but in water its solubility is less than 1 : 50,000. Its melting point is 57°C.

Although Egressin has little action on earthworms, *Ascaris* and *Enterobius in vitro*, Eicholtz recorded its action on the oxyurid species *Passalurus ambiguus* of the rabbit. A single dose of 0·1 gm./kgm. usually removed 100 per cent. of these worms. When a dose of 0·4 gm./kgm. was given for ascarid infections of the cat [species of worm not stated] some worms were evacuated. "*Ancylostoma* of the cat" required a larger dose and "*Taenia* of the cat" a higher dose still (20 gm./kgm.). But Egressin had no action on the oxyurids of the mouse (*Syphacia obvelata* and *Aspicularis tetraptera*). Experiments with dogs showed that Egressin is not absorbed in the intestine and that neither Egressin nor its derivatives (*e.g.*, thymol) can be found in the urine. When about 12 gm. of Egressin were given to a human subject the urine remained free from phenol compounds. These facts suggest that the action of Egressin is not due to the effect of the thymol in it acting as thymol and this is supported by the fact that the cat, which is sensitive to thymol, tolerates Egressin extraordinarily well (*e.g.*, in doses of 0·05–0·1 gm./kgm.). An enormous dose of 20 gm./kgm. given by the mouth to the cat produced only slight sleepiness. This dose filled the cat's stomach to its full capacity. The Egressin was evacuated with the faeces as white crystals. Further pharmacological results will be published elsewhere.

Egressin was given to ten human volunteers. A single dose of 6 gm. was well tolerated. Later it was found that in persons with slight gastritis or with an empty stomach a dose of 2 gm. of Egressin might cause slight stomach troubles or a tendency to vomit. Children given 4 gm. suffered no toxic effects. Sometimes delicate children after the normal dose suffered slight loss of appetite, or slight sleepiness on the day of the dose. One-third of the adults given the drug suffered from diarrhoea. In three heavy cigarette smokers

Egression caused nausea and vomiting. Also when strong alcohol or much fat were taken at the same time as the Egressin, after-effects followed, because of the solubility of the drug.

The action of Egressin was studied on children and adults who were patients in the Heidelberg University Orthopaedic Institute and another hospital, suffering from various illnesses. The effects of single doses were tested by giving children aged two to 12 years a single dose of 1 gm. and patients over 12 and also adults a dose of 2 gm. The effects of repeated doses were also tested by giving children between two and 12 years old three doses of 1 gm. for two days and older patients three doses of 2 gm. for two days, followed by a purge on the third day. The air in the hospital ward was found to be free from *Enterobius* eggs, so that infection from the air during the treatment and subsequent anal examinations could be excluded.

In the first series of tests, Egressin was given to 24 patients. It was given to children as a powder in their food and to the adults either in the food or coffee, care being taken that the food or drink was not hot enough to melt the Egressin. If the drug does melt, it tastes very badly and adheres a long time to the mucosa of the mouth. It is recommended that the Egressin tablets be broken up in a cup of cold water before they are given in cold coffee, marmalade or tea ; children take it best in ices. Of the 24 patients, nine children and nine adults were confined to bed, four children and two adults were ambulant.

The existing anal and vaginal itching and the consequent loss of sleep and the bedwetting of three out of five cases disappeared after three doses. On the second day of dosage after the purge large numbers of *Enterobius*, most of them dead, were evacuated and those still alive were feeble. Blood examinations done twice a week showed no change, except that any eosinophilia present disappeared. In several cases three days after the last dose the eosinophils increased to double or three times normal, sometimes rising two to five weeks after the doses to 12 or 14 per cent. In those still passing eggs after treatment there was an eosinophilia of 22 per cent. and a second treatment restored the eosinophil count to normal and removed all the worms. No worms were passed by 95 per cent. of the patients for three to eight weeks after treatment ; of these 40 per cent. remained negative for three months and a second treatment cured 5 per cent. of them. Spreading the single doses of 1 or 2 gm. of Egressin over several hours does not give results. It was noteworthy that in some cases *Enterobius* eggs appeared again regularly after the third week after Egressin. The authors suggest that Egressin does not act on the larvae of *Enterobius*. This is in accord with the work of ENIGK (*Ztschr. f. Tropenmed. u. Parasit.*, 1949, v. 1, 259), who found that for *Oxyuris equi* of the horse it was necessary to give one remedy (allegan) for the adult worms and another (phenothiazine) for the larva. Some eggs passed were empty. The question whether this meant that the larvae hatched from them had re-invaded the patient's alimentary canal was not determined.

In the second series of trials only anal swabs were taken and the number of *Enterobius* eggs on the Cellophane tape was counted. Eggs were also divided into those with granular protoplasm, those containing larvae and empty ones. In this series 35 patients were treated, chiefly children. Of these 90 per cent. gave negative anal swabs three to six weeks after treatment. In 34 per cent. eggs appeared again after four to six weeks, but there were so few that the patient suffered no annoyance. For four months after treatment 57 per cent. of the patients remained negative and in 10 per cent. a second treatment failed. Good results were obtained in private practice with Egressin given to more than 200 persons with chronic infestations. Four out of five of these infected also with *Ascaris* passed one *Ascaris* each in the stool. But it is recommended that,

in the heavier infestations, a second treatment should be given 14 or 21 days after the first. Thus Egressin is a non-toxic and effective advance in the treatment of enterobiasis. *G. Lapage*

TALICE, R. V. Épidémiologie de la trichinose. [**Epidemiology of Trichinosis.**] *Bull. Soc. Path. Exot.* 1950, v. 43, Nos. 5/6, 288–90.

DEFICIENCY DISEASES

CORKILL, N. L. **Malnutrition in Sudanese Millet Eaters : a Follow Up.** *J. Trop. Med. & Hyg.* 1950, June, v. 53, No. 6, 125–36. [14 refs.]

In 1934 [this *Bulletin*, 1935, v. 32, 465] the author described a syndrome of multiple avitaminosis, dominated clinically by burning pains (pyralgia) in the extremities, night blindness, sore mouths and weakness, among a desert community. The seasonal incidence of the sickness was related to seasonal variation in diet, there being available during the rains plenty of milk, meat and green leaves whereas in the dry season the diet was almost exclusively millet.

The region was re-visited in two seasons 12 years later, in 1945–46, and substantially similar conditions were found to prevail. Evaluation of the diets of five families indicated deficiencies of animal protein, riboflavin and vitamins A and C during the dry season. Pyralgia was found to be much less common in those who took part of their millet as beer than in those who did not brew.

Of the persons examined in 1933 a high proportion were traced in 1945, and the intervening medical histories obtained are compatible with the polyhypovitaminosis syndromes shortening life.

The inter-relationship of protein and vitamin deficiencies is discussed.

Dean A. Smith

PETERS, W. **Observations on the Vitamin B_2 Complex Deficiency Syndrome in West African Soldiers.** *J. Roy. Army Med. Corps.* 1950, June, v. 94, No. 6, 293–301. [12 refs.]

Evidence of vitamin B_2 complex deficiency was found in 70 of 929 West African soldiers examined in Accra. Glossitis was the commonest manifestation, being observed in 80 per cent. of the 70 cases. Scrotal dermatitis was present in 68·6 per cent. angular stomatitis in 37·1 per cent. and cheilosis in 14·3 per cent.

Evaluation, by calculation, of the ration scales did not suggest a serious dietary deficiency of riboflavin or of nicotinic acid, but many men found some of the items, particularly groundnut stew, unpalatable and did not eat them, and it was mainly among these men that the cases of deficiency were seen.

Dean A. Smith

SPRUE

DAVIDSON, L. S. P. & FOUNTAIN, J. R. **Incidence of the Sprue Syndrome with some observations on the Natural History.** *Brit. Med. J.* 1950, May 20, 1157–61.

Food rationing in Great Britain afforded an opportunity of assessing the incidence of those conditions requiring special dietary accommodation. Before

a dietary concession was afforded to a patient with alleged steatorrhoea, his medical attendant had to supply details of the patient's condition and the result of a chemical analysis of the stools. All cases of steatorrhoea ("sprue syndrome") were referred to a committee of which the senior author was a member; where doubt about the diagnosis existed the patient's doctor was asked to amplify his information.

Between January 1943 and December 1948, claims were received on behalf of 2,044 cases of steatorrhoea; 1,303 were cases of coeliac disease, 311 idiopathic steatorrhoea, and 403 tropical sprue, while the remaining 27 were unclassified owing to inadequate information. The number of cases of tropical sprue during this period was 44 in 1943, 81 in 1944, 129 in 1945, 87 in 1946, 34 in 1947, and 28 in 1948. There was a comparable variation in the annual incidence both of coeliac disease and of idiopathic steatorrhoea; one explanation of this is that the rise and fall in numbers was not due to new cases, but to a first application of old-standing cases for priority rationed foods such as bananas when these were advertised as available. The fall in the apparent incidence of idiopathic steatorrhoea and of coeliac disease in 1947 equally might be due to the belief that previously rationed foods were more plentiful and so claims were no longer lodged; 1948, however, dispelled this optimistic view and so the number of claims again rose sharply. The wide annual variations in these records of cases of steatorrhoea over the whole period make it difficult to assess their true incidence. On the figures the three-year period 1946–48 appears to afford the most nearly correct picture of the situation, and on these the average annual incidence of coeliac disease was 117 cases (1 in 135,000 of the population below 15 years), and that of idiopathic steatorrhoea was 44 cases (1 in 700,000 of the population over 15 years). The majority of the cases of tropical sprue were former members of the Services; the figures were governed by the military activities in "sprue zones", and by the return home of service sick either as a result of invaliding or of the end of hostilities.

The figures for the three categories of steatorrhoea for England and Wales, and for Scotland, are set out in tables; there is also a table showing the regional incidence of steatorrhoea in Scotland, where the incidence per million of population was notably higher in the West and South-East regions—possibly because greater facilities existed for full investigation and accurate diagnosis. Other causes of steatorrhoea in England and Wales are analysed and are set forth in a table; of these, diseases of the pancreas and resections of the gut or short-circuiting operations account for the bulk.

There were 517 cases of coeliac disease in males and 560 in females; the ratio, corrected for differences in the male and female populations, is 1·1 to 1·0. The corrected female-male ratio for 142 females and 103 males suffering from idiopathic steatorrhoea was 1·2 to 1, again an equal sex distribution.

A sample population of members of the R.A.F. admitted to hospital on account of "sprue" showed that only 5 per cent. of them were invalided from the service on account of it. Figures obtainable for the Army showed 342 men to have been discharged on account of tropical sprue between 1943–47, and another 30 for idiopathic steatorrhoea. "Sprue" cases in the Indian Army steadily increased in number between 1939–44 among both the British troops and the Indian. The incidence per 1,000 among British officers ranged from 0·3 to 2·6; among other ranks it ranged from 0·1 to 1·2. In Indian officers it ranged from 0·4 per thousand to 1·3, and in Indian other ranks from 0·0 to 0·2. The prognosis in tropical sprue is good; though 1,073 ex-soldiers were invalided to Britain for sprue between 1943 and 1946 there was only a very small residue of civilians receiving priority rations for this complaint in 1947 and 1948 (34 and 38 cases respectively).

The relationship of coeliac disease of childhood to idiopathic steatorrhoea of adult life was investigated by further inquiry into the previous personal histories of 100 cases of the latter condition ; a control group of 100 normal adults was subjected to the same questionary. A conservative estimate of 34 per cent. of those with idiopathic steatorrhoea gave a history of coeliac disease (five cases) or of a suggestive alimentary disorder (29 cases) in youth ; in only three controls was there a comparable history of alimentary disorder. The familial incidence of steatorrhoea was also investigated and 9·2 per cent. of 130 patients questioned gave a family history of the same trouble (usually a brother or sister with coeliac disease), while 3·8 per cent. had relatives with a condition suggestive of some type of steatorrhoea. The figures suggest that a genetic factor, possibly a recessive gene yielding a diathesis, is involved ; but environmental influence cannot be excluded. The obvious opportunity of following up cases of coeliac disease and of determining their fate is being seized.

A. R. D. Adams

EPIDEMIC DROPSY

CHAUDHURI, R. N. & CHAKRAVARTY, N. K. **Treatment of Epidemic Dropsy.** *Indian Med. Gaz.* 1950, Apr., v. 85, No. 4, 165–72. [26 refs.]

This is a well-thought-out article by members of the Epidemic Dropsy Enquiry bringing our information up to date. Sanguinerine, believed to be the toxic principle of argemone oil, has been shown by animal experiment to cause capillary dilatation and permeation and to interfere with oxidation of pyruvic acid, analogous in action to deficiency of vitamin B_1 "which produces its symptoms by interfering with cell nutrition as a result of the blockage of carbohydrate metabolism at the pyruvic acid stage, with the difference that sanguinerine blocks the sulphydryl radical of a main enzyme, thus leaving therapeutic administration of vitamin B_1 ineffective".

Rational treatment should be based on the following data : (i) The adulterant argemone oil is the primary cause of epidemic dropsy ; (ii) It is a cumulative poison ; (iii) It causes capillary dilatation and permeability ; (iv) Serum-albumin and calcium are reduced while serum-globulin is increased ; (v) Carbohydrate metabolism is checked at the pyruvic acid stage ; (vi) Myocardial damage is set up. Hence, mustard oil, unless known to be pure, should be excluded ; the patient should stay in bed to minimize the heart action, the diet should be rich in protein and with little salt ; vitamins C and P counteract the capillary changes and the consequent tendency to haemorrhages and vitamin D should be given for the calcium deficiency, so yeast tablets with cod- or shark-liver oil and citrus fruits are given. As regards drugs, diuretics and laxatives aid elimination. Antihistamines, as phenergan, have benefited because, though no rise in blood histamine has been demonstrated, the signs are suggestive of over-production. Those who have had one attack are prone to others, and it would be well to make the disease notifiable. If argemone plants cannot be exterminated, careful inspection of seeds supplied to mustard oil factories should be carried out or some method of regular detection and removal of the toxic oil.

H. Harold Scott

VENOMS AND ANTIVENENES

TAYLOR, E. H. **The Snakes of Ceylon.** *Univ. of Kansas Sci. Bull.* 1950, Mar. 20, v. 33, Pt. 2, No. 14, 519–603, 26 figs. on 14 pls. & 3 text figs.

SMITH, H. M. & TAYLOR, E. H. **Type Localities of Mexican Reptiles and Amphibians.** *Univ. Kansas Sci. Bull.* 1950, Mar. 20, v. 33, Pt. 2, No. 8, 313–80.

BOQUET, P., DWORETZKY, M. & ESSEX, H. E. **Physiologic Responses of certain Animals and Isolated Preparations to Mixtures of Snake Venom and Egg Yolk.** *Amer. J. Physiol.* 1950, June 1, v. 161, No. 3, 561–72, 5 figs. [11 refs.]

REMINGTON, C. L. **The Bite and Habits of a Giant Centipede** (*Scolopendra subspinipes*) **in the Philippine Islands.** *Amer. J. Trop. Med.* 1950, May, v. 30, No. 3, 453–5. [13 refs.]

This short paper is very interesting. Though it deals chiefly with *Scolopendra subspinipes*, more than a dozen species of centipedes are named and the results of bites [stings] by them on laboratory animals—mice, rats, guineapigs, rabbits and birds. They may cause death of these animals but, though very painful for a time, no fatality was caused among men. [Stitt states that the larger specimens may cause death in children and PINEDA recorded (*J. Philippine Islands Med. Ass.*, 1923, v. 3, 59) the death of a child, 7 years old, 29 hours after being stung on the head.] The species common on Leyte Island, *Scolopendra subspinipes*, is 11–18 cm. in length. They frequent the soldiers' tents and the screened latrine shelters where many may be found dead after DDT spraying of the buildings. They also climb the tent-walls, cling by their anal feet and swing their bodies from side to side, feeding on the insects attracted by the electric light and entering at the ventilation hole. The sting was fatal to mice but not to guineapigs. The author himself was stung in the axilla by one of these in his bed. The pain was intense for some 20 minutes; next morning the axilla was swollen and tender and the pain did not completely disappear for about three weeks.

The usual treatment is by application of ammonia, but injection of local anaesthetics, as used by dentists, gave quick relief. Toxic symptoms include headache, vomiting and rise of temperature, but these are transitory.

H. Harold Scott

DERMATOLOGY AND FUNGUS DISEASES

WINER, L. H. **Histopathology of the Nodose Lesion of Acute Coccidioidomycosis.** *Arch. Dermat. & Syph.* 1950, June, v. 61, No. 6, 1010–24, 10 figs. [Refs. in footnotes.]

Erythema nodosum is an allergic manifestation which occurs in some cases of coccidioidomycosis. According to SMITH [this *Bulletin*, 1940, v. 37, 882] it is found in only about 5 per cent. of all cases of the disease, but GOLDSTEIN and LOUIE (*War Medicine*, Chicago, 1943, v. 4, 299) reported it in 25 per cent. of their series of cases. It occurs in a much higher proportion of cases of the disease in white women than in white men and it has never been reported in persons of pure negro descent. Erythema nodosum is a very favourable prognostic sign in coccidioidomycosis, and it is also noteworthy that the tendency for the disease to progress to the grave coccidioidal granuloma stage is extremely low in white women but is greatest in the negro race.

The author made a histopathological study of erythema nodosum on 4 cases of coccidioidomycosis, 1 of tuberculosis and 4 of streptococcal infection, drug effect or unknown cause. In all cases the lesion presented the same histological picture : the capillaries in the more superficial part of the dermis were dilated and surrounded by zones of oedema. However, the most striking changes were seen in the fibrous trabeculae of the subcutaneous fat layer ; in these the larger blood vessels showed marked proliferation and separation of their endothelial lining, the muscularis was dissociated by intense oedema and infiltrated by polymorphonuclear leucocytes, and the adventitia merged into the septal fibrous tissue. There was no actual obstruction of the arterioles or loss of elastic tissue. The areolar septa showed fibrinous necrosis and an infiltration of polymorphonuclear cells and eosinophils. The walls of the smaller vessels showed hyalinization, and adjacent to these were little granulomata of reticulo-endothelial cells. At the margins of the septa masses of polymorphonuclear cells were seen in various stages of degeneration and among these were numerous mononuclear and multinuclear phagocytes. The resemblance of the reaction to the lesion of periarteritis nodosa was remarked.

J. T. Duncan

COHEN, R. & MILLER, L. **Inhibiting Concentration of Chloromycetin against** *Coccidioides immitis*. *Ann. Western Med. & Surgery*. 1950, July, v. 4, No. 7, 342–3, 1 fig.

To study the action of chloromycetin *in vitro* on *Coccidioides immitis*, bacto-tryptose agar slants and blood agar plates and slants were used. Chloromycetin was introduced in serial concentrations from 5 to 2,000 μgm./ml. Controls of plain blood agar were also used.

Material was obtained by aspiration of proved coccidioidal abscesses. In one series, this material was sown on to the medium as soon as it was aspirated : in a second series, the material was first diluted 1/10 with saline before inoculation of the media.

The results are shown in four tables and a photograph. It appears that *C. immitis* shows slight sensitivity to chloromycetin in concentrations of 1,000 and 2,000 μgm./ml. The latter concentration caused the formation of small discrete colonies, unlike the lower concentrations where spreading and confluence occurred.

H. J. O'D. Burke-Gaffney

HEAT STROKE AND ALLIED CONDITIONS

ELLIS, F. P. **The Upper Limits of Warmth tolerated by Man without Loss of Efficiency. Experimental Studies at Singapore.** *Med. J. Malaya*. 1950, Mar., v. 4, No. 3, 175–89, 1 fig. on pl. [58 refs.]

A general discussion and review of the literature.

BEERSTECHER, E. **The Effects of Tropical Acclimatization upon the Female Menstrual Cycle.** *Amer. J. Trop. Med.* 1950, May, v. 30, No. 3, 469–71.

This paper is the result of a study of 192 United States Army nurses who had been transferred directly from temperate zones in the United States to New Guinea (Milne Bay). The base was hot and humid throughout the year, and nutrition was excellent among the nurses. Ages ranged from 21 to 43 years, with an average of 28, and with 68 per cent. of these studied in the 23–30 age group. Unmarried women made up 88 per cent. of the series : 98 per cent.

were American born and 86 per cent. had always lived in the northern part of the United States. At the time of the survey the group had been in the tropical base for an average of five months, individuals having been there for one to eight months. Ninety-six per cent. were taking a grain and a half of mepacrine daily, and the remainder a similar amount of quinine [a very small prophylactic dose].

The average length of the menstrual cycle before arrival in the tropics was 27·7 days ; after an average of 5 months' residence the mean was 26·9 days, the decrease being almost entirely due to increase of 22–27 day cycles. Acclimatization did not appear to prolong the duration of the period, rather the reverse.

Twenty-six per cent. of the entire group had previously suffered from menstrual disorders, and of these, 63 per cent. reported that their symptoms were worse in the tropics. After an average of five months at the base, 45 per cent. of the entire group reported that they were suffering from menstrual disorders, the entire increase being due to dysmenorrhoea. Thirty-two per cent. reported an increased loss and 13 per cent. a diminished one. Six subjects reported intermenstrual bleeding, four of whom had never had this symptom previously. Four of the 192 subjects reported an increased sex desire and three a diminished one.

One to three months tropical residence had little effect in producing any menstrual changes and four to six months were needed for changes to occur. Age, nationality and marital state had no influence. The author considers that gynaecological disorders do not seem to constitute a serious problem in tropical acclimatization.

[An average of five months in the tropics is hardly long enough to give conclusive results. The after-effects of malaria are not dealt with.]

C. F. Shelton

MISCELLANEOUS DISEASES

BONNET, P. Sur l'utilisation possible de quelques plantes diurétiques et anthelmintiques d'Indochine. [**The Potential Use of some Diuretic and Anthelminthic Plants of Indo-China.**] *Rev. Méd. Française d'Extrême-Orient.* 1942, Mar., v. 20, No. 3, 460–70.

CASTELLANI, A. **Little Known Tropical Diseases.** *Anais Inst. Med. Trop.* Lisbon. 1949, Dec., v. 6, 369–533, 10 charts & 74 figs.

In this paper, the author collects under one cover notes on a very large number of tropical diseases which, it is stated, are not well known, partly because they are often of a minor nature and partly because many of them have not received wide publication. Their principal interest lies in their relation to differential diagnosis and the resemblance which some of these diseases may bear to more common specific conditions.

The subject is treated under the headings (1) climatic diseases, (2) fevers, (3) internal diseases, (4) diseases of the genito-urinary system, (5) diseases of the organs of special sense, (6) surgical diseases, (7) diseases of the skin. The notes in each case vary from a few lines to a number of pages and they are profusely illustrated with photographs, tables and drawings. Very many of the conditions have been described by the author elsewhere, but they are now classified in a lengthy article of over 160 pages, which cannot readily be abstracted.

More than half of the paper is occupied by descriptions of skin diseases, many of them due to fungi. This section includes notes on various ulcers, including the classical tropical ulcer. In this last connexion the statement is made that "penicillin does nothing at all, notwithstanding the many favourable reports published. The new antibiotics also do little or nothing." [Many studies abstracted in this *Bulletin* do not support this statement.]

For the large amount of information appearing in this paper, those interested should consult the original. It should, however, be observed that many of the diseases described are well recognized and a considerable proportion have been included by the author and CHALMERS in their *Manual of Tropical Medicine.* *H. J. O'D. Burke-Gaffney*

SQUIRES, B. T. **Onyalai in the Bechuanaland Protectorate.** *Trans. Roy. Soc. Trop. Med. & Hyg.* 1950, May, v. 43, No. 6, 667–72.

In this article the author records his clinical experiences of onyalai in the Bechuanaland Protectorate. There are several interesting findings, both clinical and haematological, worthy of mention.

In a series of 35 cases (22 males and 13 females) one-third of the patients were under 11 years of age [the author states "two-thirds," but the table shows 11 out of 35]. There were 3 deaths in the series (8 per cent.), all occurring in the age group of 1–10 years. Relapses were noted in 3 cases. The author has encountered mild as well as severe cases and remarks that "however grave the condition may appear, so long as there is no macroscopic haematuria, they will recover; conversely if an apparently mild case develops haematuria the prognosis becomes correspondingly serious." [This is apparently a new observation, although it is not borne out in the reviewer's experience of the disease as seen in Southern Rhodesia.] In the absence of a previously reported controlled series, the importance of blood in the treatment of the disease is difficult to assess since most cases in any event recover.

The aetiology of onyalai in the author's experience is still obscure. He is not prepared [and correctly so in the reviewer's opinion] to attribute it to a poison derived from the administration of indigenous medicine. Nor does he favour any correlation between the disease and malnutrition. He could trace no seasonal or topographical influence on the incidence of the illness.

The bulla would appear to be an essential lesion of the syndrome, for even in mild cases (the author records in addition 71 mild or atypical ones) careful search revealed its presence. He does admit, however, that onyalai may occur in the absence of bullae. A point worth mentioning is that no cases in which death could have been attributed to cerebral haemorrhage have been seen in the territory.

With regard to blood examination, the author finds a constant thrombocytopenia (the platelets varying from 5,000 to 20,000 per cmm.), the bleeding time being prolonged with a normal coagulation time. *M. Gelfand*

PROTOZOOLOGY: GENERAL

VON BRAND, T. **The Carbohydrate Metabolism of Parasites.** *J. Parasitology.* 1950, June, v. 36, No. 3, 178–92. [107 refs.]

This is an interesting summary of the subject indicated in the title by an author who has himself contributed much to this field of study. He emphasizes the importance of this type of metabolism in endoparasites [perhaps to the

exclusion of other metabolic processes]. From this substrate energy is readily obtained both under aerobic and anaerobic conditions by some parasites with resultant complete or incomplete oxidation. Environmental factors, such as availability of oxygen, are apparently not always decisive in determining which course metabolism shall follow. For some reason not understood, parasitic worms and protozoa frequently bring about incomplete oxidation of carbohydrate in conditions apparently favourable to the complete breakdown, and this fact must be related to their biochemical composition. It is suggested that the pathogenic characters of these organisms may be thereby influenced. Many parasites, including African trypanosomes, some filariae and schistosomes, which metabolize carbohydrate to a considerable extent, but fail to store it, are dependent on readily available supplies from the host. When it is freely supplied in the diet of the host a rapid increase in numbers at least of intestinal inhabitants may result. On the other hand, other species of parasites and certain worms in particular which live under conditions where no ready source of oxygen is available, possess large endogenous sources of carbohydrate, chiefly glycogen. The evidence suggests that it is derived from carbohydrates in food rather than from protein or fat. Apart from serving as a food store carbohydrate may be used in the laying down of chitinous exoskeletons. From the quantitative aspect there are enormous differences in the amount of carbohydrate metabolized by different species. Thus *T. rhodesiense* consumes approximately its own weight of glucose within a few hours, whereas negligible quantities are used by the blood forms of *T. cruzi*. An accompanying table indicates the amounts consumed by various helminths. The products of parasite metabolism are varied, thus *Bact. coli* and *Trichomonas foetus* produce hydrogen, and carbon dioxide is produced by many organisms including malarial parasites, trypanosomes and leishmania, but in widely differing amounts. Among the products of glucose metabolism a number of fatty acids, dicarboxylic acids such as oxalic and succinic as well as ethyl alcohol and glycerol have been described. The products and the proportions under which they are formed vary with aerobic or anaerobic conditions. Under the latter a series of phosphorylations, described as the Embden-Meyerhof scheme, result in the formation of lactic acid *via* pyruvic acid from glucose, and this sequence of reactions apparently occurs in malaria parasites and trypanosomes. The Krebs hypothesis accounts for the complete oxidation of pyruvate, an important intermediate in the breakdown of carbohydrate. The problem of carbon dioxide fixation by parasitic organisms awaits further investigation. *J. D. Fulton*

MOULDER, J. W. **The Oxygen Requirements of Parasites.** *J. Parasitology.* 1950, June, v. 36, No. 3, 193–200. [48 refs.]

The author accepts the definition of respiration as "the sum total of the chemical reactions carried out by the living cell which results in the liberation of energy." These energy-yielding reactions may occur under aerobic (molecular oxygen taking part) or under anaerobic conditions. In the former hydrogen atoms activated by the appropriate enzymes (dehydrogenases) combine with molecular oxygen (also activated) to give water. The enzyme systems of parasites vary widely and some are not furnished with the complete system of higher animals. On the other hand the nature of some oxidative enzyme systems of parasites doubtless remains to be discovered. Anaerobic respiration generally occurs without functioning of the cytochrome-cytochrome oxidase system, hydrogen being transferred from one substrate to another without the intervention of oxygen. Experimental evidence suggests that in plasmodia and some trypanosomes oxygen is utilized through a heavy metal

respiratory enzyme, since inhibition of respiration is effected by such substances as cyanide and carbon monoxide. Glucose is metabolized more slowly and less oxygen is used by those trypanosomes which are sensitive to cyanide than in those which are insensitive to this substance. These properties are correlated with the division of trypanosomes into different groups on the basis of morphology and differences in the life cycle as suggested by HOARE and COUTELEN [this *Bulletin* 1933, v. 30, 778]. The suggestion is put forward that trypanosomes insensitive to cyanide may have lost their heavy metal catalysts as a result of resorting to a parasitic life, but that such catalysts have subsequently been replaced by other respiratory enzymes which cause an increased rate of oxygen consumption. In certain parasitic worms, dehydrogenases are known to be present along with cytochromes. Whether the cytochromes function in the normal manner is not yet clear. Thus BUEDING [this *Bulletin*, 1949, v. 46, 763] was unable to demonstrate cytochrome in the filarial worm *Litomosoides carinii*. A table is appended in which parasitic helminths are grouped according to the effect exerted on them by cyanide. They possess porphyrin pigments resembling haemoglobin which combine reversibly with oxygen, and are synthesized by the worms themselves. Phosphorylation reactions occur during sugar metabolism in many parasites and energy can be stored as high phosphate-bond-energy compounds.

In relation to their oxygen needs, parasites have been classified in three groups as obligate aerobes, obligate anaerobes and facultative anaerobes. The blood forms of trypanosomes, malaria parasites and the filarial worm *L. carinii* apparently require oxygen for survival, but in some cases high tensions of this gas affect growth and respiration adversely. Nevertheless under anaerobic conditions they can effect glycolysis of carbohydrate. It has been reported that the eggs of certain nematodes require oxygen for development which can, however, be dispensed with by the adult worm. *E. histolytica* was believed to be an obligate anaerobe but recent work has shown that it can exist under low oxygen tensions. Possible causes of toxic effects of oxygen on parasites are outlined by the author, including loose combination with or oxidation of an essential enzyme, growth factor or substrate or production of toxic substance such as hydrogen peroxide, which LASER [*Biochem. J.*, 1944, v. 38, 333] showed was formed by *Ascaris suis* maintained under high oxygen tensions. For the fuller understanding of the toxic effects of oxygen a more detailed knowledge of the enzyme structure of parasites appears to be necessary. *J. D. Fulton*

BUEDING, E. **Effect of Drugs on Metabolism and Enzyme Systems of Parasites.** *J. Parasitology.* 1950, June, v. 36, No. 3, 201–10. [71 refs.]

Recent advances in knowledge of the physiology of parasites has helped towards a better understanding of the mechanism of action of chemotherapeutic agents. As early as 1914 the view was put forward that aniline dyes exerted their effect on bacteria through action on intracellular enzymes. In more recent years the important observation that *p*-aminobenzoic acid inhibited the action of sulphonamides on bacteria indicated the competitive nature of enzyme inhibition and was a source of much fruitful study. Some enzymes are known to function through —SH (sulphydryl) groups and may be readily inactivated by combination of these groups with such substances as trivalent arsenicals and antimonials (a similar reaction would result from the pentavalent types *in vivo*, since the latter are readily reduced to the trivalent state). Such a reaction is in keeping with the chemotherapeutic effect of these compounds in trypanosome infections. Recent observations on the effect of arsenicals on *T. evansi* and *T. equiperdum* [this *Bulletin*, 1948, v. 45, 495, 773] have indicated

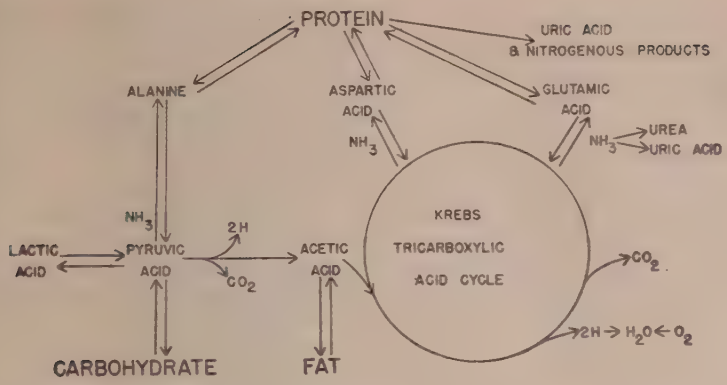
that hexokinase is involved ; this is a sulphydryl enzyme, which brings about the phosphorylation of glucose as a first step in its utilization. These observations furnish an explanation of the lethal effect of arsenicals on the parasites, for which carbohydrate is essential. *T. cruzi* shows little sensitivity to arsenicals and behaves differently in other respects to the species mentioned, which suggests that it is probably independent of a sulphydryl enzyme. No evidence could be obtained that normal and arsenic-resistant trypanosomes differed in —SH content [this *Bulletin*, 1948, v. 45, 690]. Glucose metabolism, acid production and oxygen utilization in both types were also found to be similar [*ibid.*, 1938, v. 35, 709], indicating that the enzyme systems of resistant forms were probably unaffected. The explanation of their different susceptibilities to the drug has been shown to depend on the fact that arsenic is not absorbed by resistant forms. The mechanism of the trypanocidal effect of the non-metallic diamines has not been settled, but interference with pyruvate metabolism of *T. evansi* and denaturation of nucleoproteins has been reported. Bayer 205 which is inactive against trypanosomes *in vitro* is probably converted to an active agent in the body. In the same way paludrine [proguanil] appears to be activated *in vivo*, whereas quinine, atebrin [mepacrine] and chloroquine are effective in suppressing growth of *P. knowlesi in vitro*. Recent observations [this *Bulletin*, 1949, v. 46, 445 ; 1950, v. 47, 118] provide evidence that the aerobic sugar metabolism of *P. gallinaceum* is affected by quinine. Similarly the large series of hydroxynaphthoquinones studied in America were shown to depress the oxidative metabolism of *P. lophurae*. While these substances were active in plasmodial infections of ducks and to some extent in chickens, they were rendered ineffective as a result of combination with human serum-albumin. It appears that anthelmintics have not been systematically investigated with regard to their effect on metabolic processes. Cyanine dyes have, however, been shown to interfere with the oxidative metabolism of the filarial worm *L. carinii*. [See this *Bulletin*, 1947, v. 44, 1015 ; 1949, v. 46, 763 ; 1950, v. 47, 147]. Although this class of dyes reduces the oxygen uptake of *Schistosoma mansoni*, which has a low respiratory metabolism, cyanines are ineffective in a chemotherapeutic sense against this organism, whereas they are active against hookworms with high respiratory metabolism. The wide variation in the biochemical requirements of parasitic species indicated, even in those closely related, demands a more intense study of their metabolism for the successful development of new chemotherapeutic agents.

J. D. Fulton

GEIMAN, Q. M. & MCKEE, R. W. **Symposium—Physiology of Parasites—American Society of Parasitologists, December 28, 1949. Protein Metabolism of Parasites.** *J. Parasitology*. 1950, June, v. 36, No. 3, 211–26, 1 fig. [89 refs.]

From the preceding papers of this series it is evident that the metabolic processes which take place even in the least organized parasites are extremely complex and in this discussion on the protein metabolism the authors have wisely emphasized this fact. Since proteins, with their own special characters occur in every living tissue and involve also enzyme systems and genes, great importance must be attached to their metabolism which moreover cannot be considered apart from that of the other classes of foodstuffs. The accompanying diagram by the authors helps to make this clear, and indicates the diversity of actions taking place in a cell.

Few systematic studies on the protein metabolism of invertebrates have been carried out in the past and in order to give a succinct account of the knowledge available only those studies dealing with bloodsucking arthropods, helminths



Schematic diagram of cellular metabolism. This diagram represents the coupled reactions between carbohydrate, lipid and protein metabolism that make up cellular metabolism. The parasite can affect a host cell either by competing for available essential nutrients or by producing toxic waste products.

[Reproduced from the *Journal of Parasitology*]

and protozoa are considered in the article under review. Because of their feeding habits, blood-sucking arthropods come into contact with a wide variety of infectious agents and their metabolism assumes a more than theoretical interest on this account. The presence of various enzymes and the fate of haemoglobin in these arthropods have been studied by a number of workers. Excretory products of protein digestion which have been detected are ammonia, urea, uric acid and allantoin. Tracer studies have been ingeniously applied to investigate the synthesis of radioactive silk. As, in the case of arthropods, there is a paucity of information on the protein metabolism of helminths, consideration is here limited to those that feed on or live in blood. Microspectroscopic investigations on the intestinal contents of worms have been made in order to decide whether blood is normally ingested and as an aid in determining its fate, by characterizing the different pigments present. For many worms it appears that blood fulfils a definite physiological need as a source of oxygen supply for other metabolic processes. Comparative studies on the proteolytic enzymes and their activity have been made in different genera. A large number of excretory products of protein digestion have been described. Because of their ready availability and the fact that they can be cultivated *in vitro* in the absence of bacteria or other cells, protozoa, pathogenic and non-pathogenic, living in plasma or within blood cells, have been intensively investigated. Thus for malaria parasites, trypanosomes and to a lesser extent leishmania, some data are available regarding the factors necessary for multiplication and growth and the metabolism especially of plasmodia has been very fully studied. Their production of the pigment haematin from the haemoglobin of the host cell and utilization of the globin with production of amino-acids is established. It appears that for the asexual stages of some plasmodial species glucose, methionine, vitamins, purines and pyrimidines, not available in the red cell, must be supplied from plasma. In the case of *P. knowlesi* *p*-aminobenzoic acid was found to be a growth promoting factor and essential metabolite for *in vitro* multiplication. A number of enzymes taking part in these metabolic processes have been characterized. The available evidence suggests that plasmodia can synthesize their own nucleic acids from simpler compounds. A plea is made for more intensive studies in this field of physiology.

[This series of 4 papers on the physiology of parasites contains a wealth of information not easily presented in summaries, and they should be read in the original by those interested.] *J. D. Fulton*

ADAMS, F. H., KABLER, P., COONEY, M. & ADAMS, J. M. **Diagnostic Tests for Toxoplasmosis.** *Pediatrics*. Springfield, Ill. 1949, Oct., v. 4, No. 4, 490–97. [14 refs.]

Toxoplasmosis occurs in the United States and other countries; the condition may be acute, chronic or latent. Only in a relatively few instances is the parasite recovered by inoculation of morbid material into animals. Other diagnostic methods include the rabbit neutralization test and the complement-fixation test: these tests require a well-equipped laboratory and are expensive. More recently the slide neutralization test and the skin test were introduced. The present investigation is an attempt to appraise the value of these four tests.

The rabbit neutralization test was done by a modification of that described by SABIN [this *Bulletin*, 1943, v. 40, 637]. The complement fixation test was slightly different from that of WARREN and SABIN [*ibid.*, 637]. The antigen was the clear supernatant fluid obtained by centrifugalizing pooled infected mouse peritoneal exudate that had been macerated by alternate freezing and thawing (five times). This was standardized by a method described but usually used in dilutions of 1 : 20 to 1 : 80. Pooled guineapig serum frozen in CO_2 was used as complement and two units of anti-sheep-cell serum as haemolysin. Four dilutions 1 : 2 to 1 : 16, of the subject's serum in physiological saline were prepared. "To each serum dilution, 0·2 ml. of antigen is added. After an interval of ten minutes, 0·2 ml. of complement diluted to contain 2 u. is added, and the mixture is allowed to remain in the icebox for 15 to 18 hours. After the mixture is warmed for ten minutes in a water bath at 37°C., 0·4 ml. of a haemolytic mixture, consisting of equal parts haemolysin (diluted to contain 2 u. (0·2 ml.) and 2 per cent. suspension of sheep red cells is added to it before it is shaken and placed in a water bath at 37°C. The usual controls are included with the tests which are read ten minutes after the controls clear."

The skin tests were performed with an antigen prepared by the method of FRENKEL [this *Bulletin*, 1949, v. 46, 402] 0·1 ml. of 1 : 500 dilution of the supernatant fluid of centrifuged frozen peritoneal exudate of Swiss mice to which merthiolate to a final dilution of 1 in 10,000 had been added was injected into the skin of the patient. A test was positive when after twenty-four and forty-eight hours there persisted any swelling or redness that was bigger than 0·5 cm., the size of the original swelling at the point of injection.

The slide neutralization test was that described by SABIN and FELDMAN (*Science*, 1948, Dec. 10, 660). This consisted in mixing equal parts of peritoneal exudate from an infected mouse and of the subject's serum, incubating at 37°C. for one hour, and examining under the high power a drop of this mixture to which a drop of saturated alcohol solution of methylene blue (*p*H 11) had been added. In the absence of antibody, 90 to 100 per cent. of the *Toxoplasma* take the stain, whereas in its presence less than 50 per cent. are stained.

The tests were done on a number of patients from the paediatric wards of the Minnesota school and colony for mentally defectives and on serum from other sources.

In one group of 53 in which the skin tests were not done, 19 gave positive results by both the rabbit neutralization and slide neutralization tests of which only 12 gave a positive complement-fixation test. Seven additional sera gave positive slide neutralization tests after the addition of a "*Toxoplasma* activator."

In a group of 143 patients in which all four tests were done, 26 were positive to the rabbit neutralization test, 33 to the slide test, 11 to the complement-fixation test, and 29 to the intradermal test. In 2 instances the slide test was the only one positive, and in 3 instances the intradermal test was negative when two or more other tests were positive.

In 5 instances in which the rabbit neutralization test was positive in 1946 and 1947 all four tests were repeatedly negative in 1948 and in another such case the rabbit neutralization test only was done in 1948 and was negative. Two of these cases were diagnosed as encephalitis and one as "rheumatoid"; they were noted as "recovered" at the time of the second test. The other three were diagnosed as haemophilia, subdural haemorrhage and toxoplasmosis without change of diagnosis at the time of the second test.

The prozone phenomenon was noted in 3 instances with the slide test; in two cases the undiluted serum was negative and 1 : 1,024 positive.

The new slide neutralization test of Sabin and Feldman appears to be the most accurate, the most economical and the quickest test available at present for the diagnosis of toxoplasmosis. *L. E. Napier*

HØLUND, T. Kongenit toxoplasmose. [**Congenital Toxoplasmosis.**] *Nordisk Med.* 1950, July 7, v. 44, No. 27, 1104–5, 1 fig.

The English summary appended to the paper is as follows :—

"A case with amaurosis, hydrocephalus and pubertas praecox is reported."

GARD, S., MAGNUSSON, S. H., WAHLGREN, F. & GILLE, G. **Congenital Toxoplasmosis : Clinical, Histopathologic and Parasitologic Observations during Life and at Post Mortem.** *Pediatrics.* Springfield, Ill. 1949, Oct., v. 4, No. 4, 432–42, 5 figs. [17 refs.]

The confirmation of the diagnosis of toxoplasmosis is usually delayed until the parasites have been identified in histological sections *post-mortem.* In some instances further confirmation has been obtained by animal inoculation. There have, however, been a number of cases in which the diagnosis has been made by animal inoculation of morbid material, *e.g.*, cerebrospinal fluid and blood, obtained during life. A number of strains of *Toxoplasma* have been obtained.

A case of congenital toxoplasmosis is reported. The infant was lethargic from birth and was fed with difficulty. She was under observation from the twenty-fifth to the forty-third day, when she died. She showed a very irregular temperature throughout observation—from 33·3° to 40·8°C. Other abnormalities were bilateral microphthalmia and chronic uveitis, hydrocephalus internus and cerebral calcifications, typical changes in the cerebrospinal fluid, liver and spleen enlargement, and hypoprothrombinaemia and eosinophilia as high as 1,500 per cmm.

The serum gave a positive neutralization test in rabbits, as also did serum from the patient's mother.

The diagnosis was confirmed by animal inoculation of the cerebrospinal fluid and liver biopsy material; 29 in 72 tests were positive with the former compared with 1 in 12 with the latter. Guineapigs and mice were used and material was inoculated intraperitoneally and intracranially. These animals are equally susceptible, but the intracranial route gives a far greater chance of establishing a diagnosis. Thus, intracranial inoculation of cerebrospinal fluid into mice is the test of choice (positive 22 out of 29 tests).

Post-mortem examination showed characteristic changes in the central nervous system, including dilatation of the lateral ventricles, a necrotic

encephalitis, granulomata in the brain and spinal cord, and *Toxoplasma* on histological section. Positive animal inoculations were obtained from brain emulsions as well as from spleen emulsions.

"The strain of *Toxoplasma* isolated (GL) seems to be serologically identical with the American strains RH and LM." *L. E. Napier*

ENTOMOLOGY AND INSECTICIDES: GENERAL

GALLIARD, H. & RIBO. Un cas de pseudo-myiase ambulatoire à *Chrysomyia bezziana* observé au Laos. [**A Case of Creeping Eruption from** *Chrysomyia bezziana* **seen in Laos.**] *Rev. Méd. Française d'Extrême-Orient.* 1941, Nov.–Dec., v. 19, Nos. 9/10, 1313–14.

GALLIARD, H., GRENIERBOLEY, J., PHIEM, N. H. Le premier cas de myiase humaine à *Sarcophaga fuscicauda* observé en Indochine. [**The First Case of Human Myiasis from** *Sarcophaga fuscicauda* **seen in Indo-China.**] *Rev. Méd. Française d'Extrême-Orient.* 1941, Nov.–Dec., v. 19, Nos. 9/10, 1311–12, 1 fig.

TOUMANOFF, C. Note sur quelques insectes aquatiques culiciphages de l'Indochine méridionale. [**Some Aquatic Insects of Southern Indo-China which are Predatory to Mosquitoes.**] *Rev. Méd. Française d'Extrême-Orient.* 1941, Sept.–Oct., v. 19, No. 8, 1051–60, 3 figs. on 2 pls.

BOHART, R. M. & INGRAM, R. L. **Mosquitoes of Okinawa and Islands in the Central Pacific.** *Navmed* No. 1055. Washington, D.C., Navy Dep., Bur. Med. Surg., 1946, ii–110 pp., 71 figs., 2 maps. [3 pp. refs.] [Summary taken from *Rev. Applied Entom.* Ser. B. 1950, June, v. 38, Pt. 6, 93.]

Notes are given on the morphology, distribution and bionomics, and usually the taxonomy and the relation to disease, if any, of more than 50 species and subspecies of mosquitos from some Pacific Island groups (Hawaii, Samoa, Marshall Islands, Caroline Islands and Mariana Islands) and Okinawa. Brief notes are included on the character of the islands and the most important mosquito-borne diseases on them. The study is based on collections made by the authors and also by other workers, and methods used by the authors for collecting and preserving the material are indicated. Nearly 30 of the species appear to be endemic to some islands or groups. Keys are given to the adults and larvae of the Samoan, Caroline, Mariana and Okinawan species. Three new species of *Aëdes*, one new species and one new subspecies of *Culex* and one new species of *Uranotaenia* are described.

CHOW, C. Y. **Observations on Mosquitoes Breeding in Plant Containers in Yunnan.** Reprinted from *Ann. Entom. Soc. America.* 1949, Dec., v. 42, No. 4, 465–70.

Around Chefang, Western Yunnan, during the years 1940–1942, the author observed mosquito breeding in tree holes, bamboo stumps and in leaf axils. He gives a summary of the results in this paper and lists twenty-seven species of mosquitoes found in these various containers. The holes in the trees [which are not identified] averaged 1 metre in diameter, 15 cm. in depth and were about 6 metres above ground level. From April to October, they contained brownish-red water from which collections of mosquito larvae were made every fortnight. Of the eleven species found in the tree holes, *Aëdes albopictus*

occurred in nearly all holes on all visits; other species were rare or very rare. Larvae of *Aëdes albolateralis*, *Aëdes assamensis* and *Aëdes albopictus* appeared soon after the rainwater lodged in the holes, indicating that the eggs of these species overwinter in the tree holes.

Bamboo is the commonest plant, in this region; it is cut from 70 to 170 cm. from ground level. The holes thus left in the stumps are 10 to 27 cm. in diameter and from 12 to 30 cm. deep. Mosquito larvae of 18 species were collected from the water in the stumps. *Aëdes albopictus* appeared first and at the end of the year could still be found.

At the bases of the leaves of banana and pineapple *Harpagomyia genurostris* was the only larva found. An aroid resembling *Colocasia* also yielded *Harpagomyia genurostris* as well as *Topomyia houghtoni*. *Aëdes albopictus* larvae were found in other plant axils.

The dry winter lasts from December to March when the tree holes and bamboo stumps dry out. During February and March, 1941, bamboo stumps and the dry material from four tree holes were collected and brought indoors. In April the material was wetted and next day larvae were seen. Out of 34 sound stumps, 28 produced larvae of 6 species of *Aëdes*. These were *Aëdes albopictus*, *A. annandalei*, *A. albolateralis*, *A. harveyi*, *A. assamensis* and *A. albotaeniatus* var. *mikiranus*. The tree hole material yielded *Aëdes albocinctus*, *A. assamensis*, *A. albalateralis*, and *A. albopictus*. *H. S. Leeson*

i. JENKINS, D. W. & HASSETT, C. C. **Radioisotopes in Entomology.** Reprinted from *Nucleonics*. 1950, Mar., v. 6, No. 3, 5–14, 6 figs. [41 refs.]

ii. ——. **A Field Method of Marking Arctic Mosquitoes with Radiophosphorus.** *J. Econom. Entom.* 1949/Dec., v. 42, No. 6, 988–9.

i. Radioisotopes have been found valuable tools for several types of research and they find several uses in entomological investigations. In choosing the particular isotope, the following considerations will be relevant: (1) the choice of element will depend on whether a normal metabolite is being studied (in which case, carbon or perhaps phosphorus would be suitable) or whether the element is fixed to an insecticide (*e.g.*, Br in bromine-DDT) or whether any convenient element is used merely for "tagging" an insect. (2) The half-life of the element must be of suitable duration. (3) The type of emission required will depend on range of detection expected (normally only *beta* and *gamma* rays are used). (4) The choice is usually limited, to some extent, by availability. Generally only pile-produced isotopes are feasible as cyclotron isotopes are too costly.

The types of uses to which radio-isotopes can be put, include the following:— (*a*) Insects can be "tagged" with various radio-isotopes for studying their migrations and distribution. This is merely a refined and harmless method of marking them. (*b*) Blood-sucking and sap-feeding insects can be studied to prove whether they carry over small quantities of (radioisotope tagged) fluid from one food source to another. This has bearing on disease transmission. (*c*) Radioisotopes can be used to mark trace elements which seem to be important in resistance of certain plants to insects. (*d*) The movements of elements in the course of metabolism can be studied by making auto-radiographs of sections or parts of the bodies of insects fed on or treated with compounds containing radioactive atoms. (*e*) The sites of deposition of insecticides can be studied in the same way.

In addition to these indirect methods, the direct effect of radiation on the insect's metabolism and reproduction can be investigated. For example, the speed of reproduction and also the frequency of mutations seem to be affected by certain types of radiation.

ii. This paper gives some details on one of the uses of radioactive tracer elements. It was required to study the flight range of mosquitoes (*Aëdes pullatus* and *Aëdes excrucians*) breeding in pools in the Canadian Arctic. Radioactive phosphorus (P^{32}) in the form KH_2PO_4 was added to pools in which the mosquito larvae were breeding, to give 0·2 to 0·3 microcuries per ml. of water. At various times, larvae, pupae and adults were removed and their radioactivity determined at a distance of 1 cm. The average figures, in milliroentgens per hour, were :—

Stage	*Aëdes pullatus*	*Aëdes excrucians*
Fourth-instar larvae	6·3	7·5
Pupae	3·7	3·8
Males	1·1	1·5
Females	1·5	1·7

(Background count=0·01 mr./hour.)

It was estimated that the insects could have been detected over a period of ten weeks (five half lives of P^{32}) at which time the insects would still have given counts four times the background figure. *J. R. Busvine*

Bruce-Chwatt, L. J. & Kee Hock Ooi. **Aircraft Desinsectisation in West Africa.** *Monthly Bull. Ministry of Health & Pub. Health Lab. Service (directed by Med. Res. Council).* 1950, June, v. 9, 142–7.

Experiments with two kinds of aerosol for disinsectization of aircraft were made at Lagos Airport in Nigeria in Spring, 1950. Two kinds of aeroplane were used ; De Haviland "Doves" (400 cu. ft.) and Bristol "Wayfarers" (1,700 cu. ft.). Cages containing females of *Aëdes aegypti* and *Anopheles gambiae* were placed in three positions in the machines before treatment, and observations were made on ten-minute "knockdowns" and 24-hour kills.

The aerosols used were as follows : (*a*) a low-pressure Freon-dispersed insecticide containing 0·3 per cent. pyrethrins and 2 per cent. piperonyl butoxide (in a "bomb" produced by Messrs. Cooper MacDougall and Robertson). (*b*) Messrs. Stafford Allen's "Insecticide R587", containing 0·4 per cent. pyrethrins, which was dispersed by carbon dioxide from the Porton-Sparklet apparatus. [The exact formulae are not given and it is difficult to make a precise comparison since dosages are given in seconds per 1,000 cu. ft. ; and the bomb emits *1 gm.* per sec. while the sparklet apparatus emits *1 ml.* per sec.]

Preliminary trials showed that at five seconds per 1,000 cu. ft. both treatments gave only erratic and unsatisfactory results. Other trials may be summarized thus :—

Expt. No.	Dose (secs. per 1,000 cu. ft.)	Plane closed for (min.)	Percentages of Insects affected							
			Porton Sparklet				L.P. Bomb			
			Aëdes		*Anopheles*		*Aëdes*		*Anopheles*	
			KD	Kill	KD	Kill	KD	Kill	KD	Kill
1– 3	12·5	10	67	96	(73)	(100)	66	97	(77)	(100)
4– 6	12·5	3	41	75	(58)	(90)	48	93	(83)	(98)
7– 8	25	3	83	100	—	—	87	100	—	—
9–10	18	3	95	100	—	—	90	100	—	—

The results with *Anopheles* are given in brackets since they refer to fewer tests than those of *Aëdes*. Experiments 1 to 8 were done in "Dove" aircraft, while Nos. 9 and 10 were done in a "Wayfarer". This series of tests indicates :—

(1) A dosage of 5 seconds per 1,000 cu. ft. is unreliable for aircraft disinfestation, with aerosols of the formulae mentioned. A dosage of 12·5 seconds per 1,000 cu. ft. gave complete kill of *A. gambiae* but only partial kills of *Aëdes*. Only at 18 to 25 seconds per 1,000 cu. ft. were high knockdowns and complete kills obtained.

(2) Closure of the aircraft for ten minutes after treatment gives better results than closure for three minutes. But the shorter period is very highly desirable, owing to discomfort of passengers kept waiting in a plane, which becomes very hot on a runway in the tropics.

(3) The Low-pressure Freon bomb gave better distribution and kill than the Porton-Sparklet apparatus. [*Sic*, but the figures do not indicate a very distinct difference.] *J. R. Busvine*

DE MEILLON, B. **New South African Simuliidae (Diptera).** *Proc. Roy. Entom. Soc. of London.* Ser. B. 1950, Feb. 15, v. 19, Pts. 1/2, 14–17, 3 figs.

The males, females, cocoons and pupae of three new species of *Simulium* are described; *S. merops* from Cape Province, *S. natalensis* and *S. narcaens* from Natal. [Larvae are not mentioned.] *H. S. Leeson*

STARKOFF, O. & STARKOFF, I. Contributo alla conoscenza dell'acarofauna di Roma e dintorni. IIa nota: Sottordini *Sarcoptiformes* e *Prostigmata*. [**The Mites of Rome and its Surroundings; II Suborders** *Sarcoptiformes* **and** *Prostigmata*.] *Riv. di Parassit.* Rome. 1950, June, v. 11, No. 2, 85–101. [15 refs.]

The English summary appended to the paper is as follows :—

"The authors present a list of 100 species of mites (*Sarcoptiformes* and *Prostigmata*) found in Rome and surroundings."

WALTON, G. A. *Argas brumpti* **Neumann 1907 (Argasidae, Ixodoidea) in Kenya Colony.** *East African Med. J.* 1950, May, v. 27, No. 5, 207.

When searching for *Ornithodorus moubata* in a village of Meru District, Kenya, the author learned from the local tribesmen of another tick said to be found among rocks, but not in huts. Search in neighbouring rocky *kopjes* inhabited by hyrax revealed seven specimens of this tick. It was identified at the Rocky Mountain Laboratory, Hamilton, U.S.A., as *Argas brumpti*.

The ticks were found in hollows filled with dusty sand and hyrax droppings on the completely dry floor of deep clefts under huge rocks. The tribesmen frequently have occasion to shelter beneath these ledges of rock and they fear the tick because of the serious effects which they attribute to its bite.

This appears to be the second authentic record. The tick was found originally by BRUMPT nearly 50 years ago at the entrance to porcupine burrows at Ogaden, Somaliland. [The earliest reference given by the author is 1907: but Brumpt, in his *Précis de Parasitologie* states that he was himself bitten by this tick in Ogaden in 1901: and he refers therein to the severe nature of the bite.]

H. J. O'D. Burke-Gaffney

TOUMANOFF, C. Etude descriptive et iconographique de quelques tiques de l'Indochine. [**Descriptive Study of some Ticks of Indo-China with Illustrations.**] *Rev. Méd. Française d'Extrême-Orient.* 1941, May–June, v. 19, Nos. 5/6, 478–505, 49 figs. on 13 pls. [10 refs.]

TOUMANOFF, C. Sur une espèce de tique du gen. *Haemaphysalis* probablement nouvelle (*Haemaphysalis trispinosa.* n. sp.). [*Haemaphysalis trispinosa,* **probably a New Species of Tick of the Genus** *Haemaphysalis.*] *Rev. Méd. Française d'Extrême-Orient.* 1941, Sept.–Oct., v. 19, No. 1, 1042–3, 6 figs.

BOOK REVIEW

PIEDROLA GIL, Gonzalo. **Recientes adquisiciones y técnicas de empleo del D.D.T.** [Recent Methods and Techniques for the Use of DDT.] Prólogo del Dr. V. MATILLA. pp. xi+307, 54 figs. 1948. Madrid: Instituto Español de Medicina Colonial, Atocha 106.

This book provides for the Spanish speaking scientist, what WEST and CAMPBELL supplied for English readers; a summary of information of the uses of DDT and a reference book giving its physical, chemical and biologically-active properties.

The first chapter gives the history of the development of the insecticide, outlines its manufacture and describes the make-up of technical-grade DDT (giving a specification). The physical properties of the various isomers are given in some detail; for example, crystallographic specifications are given and illustrated. Two chapters are devoted to the toxicology of DDT, both from the standpoint of chemical constitution and from the signs of poisoning observed in insects and mammals.

Consideration is given to the estimation of DDT by chemical or physical (spectrophotometric) methods, and a long practical chapter is devoted to the preparation and use of DDT in the form of powders, solutions, emulsions and suspensions.

The author then turns to the insect pests, against which DDT can be used, and begins with human parasites and disease vectors. Experiences during and after recent wars are quoted and, in addition to the well-known Naples epidemic, some details are given of a typhus epidemic in Morocco which was quelled by DDT. Further sections deal with uses against fleas, mosquitoes and flies. The agricultural and veterinary uses of DDT are given rather briefly, many of them by means of a kind of summarizing table.

The book ends with a biography of Dr. Paul MÜLLER of the Geigy establishment, who first demonstrated the efficacy of DDT as an insecticide, and with various miscellanea, such as an account of the Naples typhus epidemic, first according to American and then from British sources.

Dr. Piedrola Gil of the *Instituto Español de Medicina Colonial* has produced a useful handbook for his compatriots at home and in the colonies and one which will be valued in those parts of South America where Spanish is spoken. Elsewhere, it will be perhaps mainly of interest to those with special interest in the insecticide DDT. *J. R. Busvine*

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